The Canadian Medical Association Journal

JUNE 1, 1958 • VOL. 78, NO. 11

CYTODIAGNOSIS IN CANCER OF THE CERVIX*

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CYTOLOGIC INVESTIGATION of cancer has been reported in the literature since the mid-nineteenth century. Donaldson[1] in 1853 described the appearances of cells in "tumour juice", while Beale[2] in 1859 described tumour cells in sputum from a case of carcinoma of the pharynx. Through the years other investigators[3-6] contributed to the cytologic diagnosis, but the data passed unnoticed, or were regarded as having little practical significance. It remained for the paper by Papanicolaou and Traut,[7] in 1943, to arouse interest in the method as a means of early diagnosis of cancer. Since then it has become an established laboratory procedure, of special value when applied to the cervix.

MATERIAL AND METHOD

The Pathological Institute at Halifax provides the histologic diagnosis of cancer for the province of Nova Scotia (pop. 660,000). Approximately 120 new cases of undoubted carcinoma of the cervix are confirmed annually. During the four-year period covered by this survey (1952-1955), over 16,000 smears from approximately 8000 patients were examined for cytologic evidence of cancer. The smears were graded as positive, suspicious, doubtful or negative for malignancy. In most cases positive and suspicious or doubtful cytologic reports were further investigated by histologic examination of biopsy or conization material. The histologic examinations were performed by one pathologist, independently of the cytological examinations, and reported as infiltrating carcinoma, undoubted carcinoma *in situ*, doubtful lesions and negative for malignancy. Results were not correlated until a histologic diagnosis had been established.

The smears were received at the Institute as fixed, unstained smears, coated with glycerin to prevent drying. Upon receipt the smears were immersed in fixative (alcohol-ether) to remove the glycerin, whereupon they were stained by hæmatoxylin and eosin as for histologic section. More complicated staining procedures designed to bring out differential staining of the cytoplasm have been discarded as being cumbersome in application and formula, and offering no advantage over well-stained hæmatoxylin and eosin preparations.

TABLE I.—ACCURACY OF POSITIVE SMEARS

	No. of smears examined	*No. reported positive*	*Histologic diagnosis*			
			Infiltrating carcinoma	*Carcinoma in situ*	*Doubtful lesions*	*Negative for carcinoma*
1952	1292	38	32	2	1	3
1953	1417	54	45	4	3	2
1954	1515	70	62	3	2	3
1955	1910	80	67	5	4	4
	6134	242	206	14	10	12

GENERAL ACCURACY OF THE METHOD

Positive Smears (Table I)

In the past few years, many workers have presented reports attesting to the accuracy of smear diagnosis. In this review, of the 8378 specimens received for cytologic examination, 6134 (73.3%) were of vaginal or cervical origin. Of these, approximately 4% were classed as showing cells of undoubted malignant origin. Table I presents the accuracy of these positive smears.

During the period covered by the survey, 12 cases of cancer of the cervix, unsuspected clinically, were diagnosed by cytologic means and later con-

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TABLE II.—OUTCOME OF SUSPICIOUS AND DOUBTFUL SMEARS

				Histologic diagnosis			
	No. of smears examined	*No. reported suspicious*	*Not followed further*	*Infiltrating carcinoma*	*Carcinoma in situ*	*Doubtful lesions*	*Negative for carcinoma*
1952.....	1292	39	11	13	1	2	12
1953.....	1417	25	6	11	3	3	2
1954.....	1515	28	5	13	1	4	5
1955.....	1910	31	8	14	2	3	4
Total.....	6134	123	30	51	7	12	23

firmed from conization material. Smears had been submitted as part of a routine physical examination. The results for the cervix confirm the value of the method as applied to this site. It is considered, moreover, that the service makes an additional contribution by increasing interest in early diagnosis of cancer.

Doubtful and Suspicious Smears (Table II)

In addition to those smears diagnosed as unequivocally positive, 123 were classed as of doubtful or suspicious nature. Of the latter, 30 were not investigated further by the clinician. The remainder were subsequently investigated by examination of biopsy or conization material, or by repeated smear examinations. The latter were followed up, where indicated, by further examination of histologic material, and a total of 58 cases were ultimately shown to be cases of undoubted carcinoma. This represents 62.2% of the suspicious and doubtful smears in which subsequent histologic investigation was carried out. Of the 30 patients with suspicious smears which were not studied further, none has returned with carcinoma.

Negative Smears

The error of cytologic diagnosis is more on the side of overdiagnosis of cellular change, thus leading to "false positives". To date, only two cases are on record in which a negative smear diagnosis was later followed by positive tissue findings of infiltrating carcinoma. There are, of course, certain insoluble factors in analyzing negative reports, as, for example, how many of these patients will develop cancer at a later date. Consequently it is impossible to draw specific conclusions as to the accuracy of the negative reports, but this too appears to be of a high order.

TABLE III.—ANALYSIS OF MATERIAL USED

Cytologic diagnosis	*Histologic diagnosis*	*Number of smears used*	*Number of cells examined*
Positive	Carcinoma (invasive).....	25	500
Positive	Carcinoma (*in situ*).....	7	140
Positive suspicious	Negative for malignancy.....	10	200
Negative	Normal tissue.....	25	500
		67	1340

SPECIAL STUDY

From the material received, a number of smears were chosen for a detailed study of the individual cells. In all cases the smear diagnosis had been followed by histologic examination of tissue. Table III presents an analysis of the material used, which encompassed cells from normal subjects, carcinoma *in situ*, invasive carcinoma, and chronic cervicitis.

The special study of cellular morphology embraced nuclear and cell diameters, nuclear and cell shapes, an examination of nuclear and cell borders, cytoplasmic changes, chromatin structure, nucleoli, and degenerative nuclear changes. Measurements of the cell and nuclear diameters were made with an eyepiece micrometer, previously calibrated against a stage micrometer, at a magnification of 1000 diameters. For the round, regular cells, two diameters at 90° were measured and averaged; for the more irregular cells and nuclei, four to six diameters were measured.

It was found convenient to subdivide the normal cells into three types—inner and outer basal cells, and superficial or "squame" cells. No attempt was made to subdivide those cells regarded as being malignant.

Nuclear and Cell Diameters

As is shown in Table IV, the maturation of the normal cells is characterized by progressive accumulation of cytoplasm, with little or no change in the nuclear dimensions. There is considerable overlapping of the various types of normal cells, and in the case of borderline cells identification becomes a matter of personal bias. To standardize the direction of overlapping, such doubtful cells were classed with those of the next (more mature) type.

The over-all range for malignant cells was not too far from that determined for the normal cells, and three-quarters of the malignant cells are encompassed by the size range occupied by cells of the normal inner and outer basal types. The abnormal but not malignant cells occupy a position approximately midway between the normal and the malignant. Thus it is seen that there is nothing in cell diameters alone that is distinctive for malignant cells, or that will permit the cytologic differentiation of malignant cells from invasive carcinoma and those from carcinoma *in situ*.

TABLE IV.—CELL AND NUCLEAR DIAMETERS

Cell type	Extreme range		Range of majority				N/C ratio
	Cell (C)	Nucleus (N)	Cell diameter	Incidence	Nuclear diameter	Incidence	
Normal							
Inner basal	22-32	10-15	23-31	68%	11-14	95%	1:2.2
Outer basal	30-57	10-18	39-53	75%	11-14	95%	1:3.0
Superficial	52-95	9-16	70-91	71%	10-13	91%	1:6.4
Non-malignant	28-48	12-30	30-42	77%	14-26	82%	1:1.6-2.3
Malignant							
Invasive	17-86	14-47	24-56	77%	16-36	95%	1:1.2-1.8
In situ	20-66	14-37	23-48	79%	15-34	96%	1:1.4-1.8

The nuclei of the normal cells show an extremely narrow range of size variation. Over 91% of all normal nuclei are encompassed within a range of only three microns. Apart from a slight reduction in size in cells of the superficial type, there is no apparent alteration of nuclear dimensions throughout the transition of normal cells from inner basal to superficial types.

Malignant cells, on the other hand, show a definite increase in nuclear dimensions which is not proportional to any increase in the cell size, so that much greater values for the nuclear/cytoplasmic ratio result. The nuclear values for the cells from chronic cervicitis again appear to fall midway between the malignant and the normal.

Nuclear and Cell Shapes

Both the cells and their nuclei could be classed into four groups—round, ovoid, elongate or angular. Among the normal cells, the shape was remarkably constant for all three types, and both cells and nuclei tended to assume a round or ovoid shape. Malignant cells revealed but little greater tendency to show variation in cell shapes, but nuclear pleomorphism was more pronounced. There was no difference between the two types of malignant cells in regard to cell and nuclear shapes. The non-malignant cells derived from cases of chronic cervicitis maintained their position midway between the normal and malignant groups, as far as nuclear and cell shapes were concerned.

Nuclear and Cell Borders

In all types of cells, the cytoplasmic boundary was well defined but not unduly pronounced. In only a small number was the cell boundary sufficiently pronounced to constitute "peripheral condensation". This condensation appeared as a bright, rather refractile rim about the extreme limits of the cell body, staining more intensely with eosin than did the rest of the cytoplasm. Condensation appeared with almost equal frequency among malignant, normal and non-malignant cells.

The most pronounced differences between normal and malignant cells were referable to changes in the appearance of the nucleus. The malignant cells tended to show nuclear borders that were wrinkled, condensed and angulated, whereas those of the normal nuclei almost invariably were smooth, unbroken and not prominent. While no differences could be made out between the two types of carcinoma cells, the cells in chronic cervicitis showed significantly more of these changes than did the normal nuclei, but not to the extent seen in malignant cells.

Cytoplasmic Changes

In addition to cells which showed peripheral condensation, a small number, occurring with equal frequency among all classes of cells, showed an arrangement of concentric rings of condensed cytoplasm. These rings were similar to those described as "peripheral condensation", but they extended throughout the cell body from nucleus to the cell border, giving a laminated appearance to the cytoplasm. Similar cells have been described in sputum by Philps,[8] who regards this as evidence of keratinization.

Cytoplasmic vacuolation was not a distinctive feature of any of the cells studied, and appeared no more frequent among malignant cells than among normal cells. However, most of the vacuo-

TABLE V.—CHROMATIN PATTERNS

Cell type	Uniform, finely granular	Finely granular with coarse clumps	Finely granular, peripheral clumps	Coarsely granular	Pyknotic
Normal					
Inner basal	95.0%	3.0%	2.0%	—	—
Outer basal	93.5%	3.5%	1.0%	2.0%	—
Superficial	71.0%	0.5%	1.0%	1.5%	26.0%
Non-malignant	53.0%	22.0%	4.0%	17.0%	4.0%
Malignant					
Invasive	24.2%	24.0%	3.8%	46.4%	1.6%
In situ	29.9%	26.3%	1.8%	41.3%	2.1%

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lated cells seen among the malignant types occurred in cases of carcinoma *in situ*.

While cytoplasmic features tended to be non-specific and to occur equally among all cell types, one feature of the cytoplasm was encountered only among malignant cells. This was the invasion of the cytoplasm by leukocytes. In the few cells showing this phenomenon, the number of leukocytes ranged from 10 to 21, often completely filling the cytoplasm. Around many of the leukocytes was a clear lytic zone, while the nuclei of the malignant cells were pyknotic and degenerate.

Chromatin Structure

Table V gives details of the chromatin architecture. Normal nuclei presented a finely granular chromatin pattern, generally associated with a normochromic staining reaction. The malignant cells showed mainly a coarsely granular pattern, and while mostly associated with a hyperchromic staining, there was also greater tendency for variation in the staining presented.

Nucleoli

Of all the cells examined, nucleoli were encountered only among malignant cells, but the number of cells showing this body was small, and in very few could it be said to be prominent. Nucleoli were seen in 5.8% of the malignant cells studied, and where identified were usually single. Double and multiple nucleoli formed only 0.4% of the nucleoli seen. A rare nucleolus was of large size and bizarre shape, measuring three to four microns in maximum diameter. Nucleoli appeared more often among malignant cells from invasive carcinoma than from carcinoma *in situ*.

Degeneration

Evidence of cell degeneration was somewhat more pronounced in malignant cells than in normal cells, but was of sufficient degree to be appreciated on visual inspection of smears in routine examination. Pyknosis among the normal cells was largely confined to the superficial cells, and consisted mainly of a shrinkage and condensation of the nuclear material. Karyorrhexis and karyolysis were seen in only 3% of the degenerating cells. Among the malignant cells the process appeared to begin at any stage in the maturation of the cell, and to proceed to karyorrhexis and karyolysis at an enhanced rate. This was slightly more pronounced among cells of carcinoma *in situ* than in invasive carcinoma. Other features of degeneration, namely nuclear fenestration and vacuolation, were again more pronounced among malignant cells, and especially pre-invasive carcinoma cells.

Other Features

In the past, considerable emphasis has been placed on the presence of "epithelial pearls", the "tadpole" and the streamer cell. That undue importance has been attached to these forms has been illustrated by Reagan and Moore.[9] In this survey, epithelial pearls were found in almost equal proportions among all types of smears. Unless the constituent cells of the "pearl" are themselves of malignant appearance, these forms have no diagnostic importance. The tadpole and the streamer cells appear to be the result of artefact when making the smear, as almost invariably the streamer portion of these cells was oriented in the direction of smearing. At any rate a maximum of 0.8% of these forms was encountered among malignant cells.

DISCUSSION

Among others, Willis[10] has expressed doubts as to the reliability of the smear method as a diagnostic aid in cancer. Our own statistics and those of other workers have demonstrated the high degree of accuracy that can be obtained. But it must be pointed out that errors do arise, and these can be attributed to one of two basic faults: a technical one arising from improper sampling of the specimen, or in procuring the sample originally, and difficulty in making a microscopic interpretation of the smear. The former is more applicable to specimens such as sputum and gastric washings, and we have encountered only one case in which sampling of vaginal secretion could be regarded as faulty. Errors resulting from microscopic interpretation are more difficult to evaluate and control. They result from personal interpretation of the cellular changes, which is bound to vary somewhat from person to person.

In regard to the latter point it is interesting to speculate on the role played by what is called "observer error". Johnson[11] has illustrated by two examples that most observers assume that the "signs" seen are present, and that those unseen are absent, while for the same observer, using the same material, the "sign" may be present at one time and absent at another. He further points out that the relevance of a sign, or its interpretation, is automatic and preconceived, so that we may ignore certain patterns, or attribute different meanings to them in accordance with past experience. All this is performed unknowingly and with the best of faith in our "judgment". Some such mechanism undoubtedly explains many of the false positive and suspicious reports. In a number of instances, while revaluating the smears for this review, those that had previously been considered as positive or suspicious were classed, unhesitatingly, as negative when examined at a later date. Both factors of observer error are implicated. "Signs", such as minor irregularities in a small number of cells, are present to the observer at the first examination and are interpreted as indicative of malignancy. At a later date, to the same observer, either the signs are absent or their

interpretation is now different. The extent to which observer error is involved is difficult to evaluate, but its effect should be kept in mind, especially in those cases where the findings are suggestive of but not conclusive for malignancy.

Many smears are unequivocal in their interpretation, either as positive or negative for malignant cells: others are doubtful or suspicious. A similar position is met in the histologic diagnosis of cancer of the cervix, and in this institute they are classified as infiltrating cancer, undoubted carcinoma *in situ*, debatable lesions, or as negative for malignancy. In 10 of the smears critically studied, the cytologic diagnosis had been an unqualified "positive", yet histologic examination failed to show carcinoma. Four of these showed a debatable lesion. Of all the smears graded as doubtful or suspicious, 62% of those followed by histologic studies showed undoubted carcinoma, either infiltrating or *in situ*, while 13% showed a debatable lesion. Thus it is seen that there exists a close parallelism between cytologic and histologic examination.

Gates, MacMillan and Middleton[12] have similarly recorded cases in which cell study revealed cells of characteristic neoplastic appearance, but for which histologic evidence was never obtained. They felt that in their cases the cytologic findings were too significant to be entirely nullified by the negative histology, and suggest that carcinoma *in situ* may present as a minute, circumscribed and slowly growing lesion, easily missed by biopsy. They further felt that in these cases, examination of vaginal or cervical smears for exfoliated malignant cells may be more reliable than biopsy examination.

There is no clear-cut separation between normal, "precancerous" and cancerous tissue, nor does malignancy arise at a single focus in time or place. It arises as a steplike deviation from normal, and as a consequence there are all gradations between normal and malignant. Malignancy can be interpreted as an exploitation of the natural proclivities of the cell and tissues, perverted and exaggerated to a point of irreversibility. Ferguson[13] has rightly pointed out that all the changes associated with malignancy in cells can be seen in nutritional, degenerative, or inflammatory reparative processes. Extreme variations in nuclear size, shape and staining properties are seen in hyperplasia of the thyroid; in liver cells these changes, as well as abundance of mitosis, are commonly associated with injury and repair. While invasion is possibly the ultimate criterion of malignancy, "invasion" nevertheless occurs on the part of normal cells in repair and healing of wounds by granulation. It is not surprising then that cells with the features of malignancy should be encountered in noncancerous conditions, and we feel that many, if not all, of our false positive diagnoses are explained on this basis.

We concur with Willis that there is no single cell measurement which will surely identify the malignant cell. Our series presents normal and malignant cells, pre-invasive malignant cells, and abnormal but not malignant cells. In all of these, measurements of cell and nuclear diameters, critical examination of the cytoplasm, nuclear boundaries, chromatin structure, the presence and configuration of nucleoli and degenerative changes, did not reveal a single characteristic which was wholly referable only to malignant cells. Further, there is nothing in the morphology which will indicate which cell will show invasive proclivities. "Positive" smear diagnosis can be made, and with a relatively high and constant degree of accuracy. But this is accomplished, not on the basis of any one specific change, or on a group of specific changes, but on general changes occurring more commonly, and in greater numbers, in malignant cells. One or a dozen cells showing morphologic changes usually associated with malignancy should excite interest for further investigation, but should not provide the basis of an unqualified diagnosis.

Cytoplasmic changes occur with equal frequency in malignant and nonmalignant cells, and are of no consequence in the evaluation of malignancy in cells. Nuclear changes are by far the more valuable, for although they occur in malignant and nonmalignant cells, the former show nuclear abnormalities in far greater frequency. Absolute increase in size of the nucleus without a corresponding increase in cell size is the greatest single aid in recognition of malignant cells. Caution is necessary here too, however. Malignant cells in our series showed a nuclear/cytoplasmic ratio ranging from 1:1.2 to 1:1.8. While in general that for normal cells was only half as great (averaging 1:2.5), an occasional cell revealed ratios close to the upper limits found for malignant cells. In cells of chronic cervicitis, the ratio ranged from 1:1.7 to 1:2.3, a range which shows considerable overlapping with that of malignant cells.

Prominence and wrinkling of the nuclear membrane are also of aid in diagnosis, but again may be seen in normal cells, as well as cells of chronic cervicitis. Increase in nuclear content as shown by hyperchromatic staining associated with a coarsely granular chromatin pattern is of importance in recognition of malignant cells, but again may be observed as a reaction to an inflammatory process.

Evidence of cellular degeneration—pyknosis, nuclear fenestration, cytoplasmic vacuolation and hyalinization—appeared more prominent among cells of carcinoma than in normal cells, and was most apparent in cells of carcinoma *in situ*. This is undoubtedly a reflection of poorer nutrition in cancerous epithelium, especially in incipient carcinoma, which occupies a superficial situation. These changes, however, are usually of insufficient magnitude to be appreciated on routine examination of smears.

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Enlarged and bizarre nucleoli, especially in combination with other nuclear changes, are of great value in establishing a positive smear diagnosis, but the number of cells showing deranged nucleoli was small, and in many smears none were present. Where seen, they tended to be of small size and single, and macronucleoli were scarce.

Mitotic figures were not noted in smears of vaginal and cervical secretions. This is not surprising when it is realized that the exfoliated cells studied in smears are dead when cast from the surface of the tumour. Under these conditions mitotic figures would not be expected in any great numbers.

Invasion of cells by leukocytes may also be referable to the casting off of dead cells by the tumour. It seems improbable that leukocytes would invade a living cell, and while the possibility of phagocytic powers by malignant cells cannot be excluded, the appearances were those of infiltration by leukocytes—the clear lytic zones around the latter suggesting lysis of the invaded cytoplasm, and the dense pyknotic nuclei of the invaded cell attesting to its death.

SUMMARY AND CONCLUSIONS

A four-year survey of the material received at the Pathological Institute, Halifax, N.S., for cytologic diagnosis of cancer of the cervix is presented. A detailed investigation into the morphology of the malignant cell has been made, and certain conclusions have been drawn.

While the error for positive smears was less than 10%, the over-all error for positive, doubtful and suspicious smears was 22%, and for this reason every positive or suspicious diagnosis should be confirmed by histologic study of biopsy specimens.

False diagnosis arises either from faulty sampling or from difficulty in interpretation of the microscopic findings. The latter generally produce a false positive or suspicious report. Observer error is probably implicated.

The diagnostic features of cells are referable only to the nucleus. Cytoplasmic changes are ill-defined and common to all the cells studied, regardless of their type. The features found to be of most value, in order of merit, are: (a) increased nuclear/cytoplasmic ratio; (b) condensation and wrinkling of nuclear membranes; (c) increased chromatin staining and alteration of the chromatin pattern to a coarsely granular type; (d) presence of macronucleoli; (e) variation in size and shape of nuclei.

Cells which are the morphologic equivalent of cancer cells appear to be formed in the cervix at least at some time during the life of many patients in whom cancer cannot be demonstrated. Cytologic diagnosis is possible only because in cancer many such cells are seen in the smear. The findings suggest that cancer proceeds in steplike deviations from normal, and that only in a small number of cases does the process reach full fruition.

I am indebted to Dr. N. G. B. McLetchie for his valuable advice and criticism during the preparation of this paper, and for the histologic diagnosis of the tissue sections.

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RÉSUMÉ

L'auteur présent une vue d'ensemble des spécimens envoyés pour diagnostic cytologique du cancer du col à l'Institut pathologique de Halifax au cours de quatre années. Une étude approfondie de la morphologie des cellules malignes permet de tirer certaines conclusions. Dans la série qui nous concerne l'ensemble des frottis positifs comportait une erreur de 10%; l'erreur totale des frottis positifs, douteux et suspects s'éleva à 22%. Il importe donc que chaque frottis considéré comme positif ou suspect soit confirmé par l'examen histologique d'un spécimen prélevé par biopsie. Les diagnostics erronnés proviennent d'un échantillonnage imparfait ou de difficultés dans l'interprétation de l'image microscopique, de sorte que celle-ci est généralement rapportée comme suspecte ou faussement positive. Les caractéristiques cellulaires qui peuvent contribuer au diagnostic se rattachent uniquement au noyau. Les altérations du cytoplasme sont vagues et communes à toutes les cellules indépendamment de leur type. Les critères les plus utiles sont (par ordre d'utilité): une augmentation dans le rapport du noyau au cytoplasme; la condensation et le froncement des membranes nucléaires; une teinture plus intense de la chromatine et une modification du réseau de cette chromatine vers un arrangement plus granulaire; la présence de macronucléoles, et enfin, une diversité dans la taille et la forme des noyaux. Des cellules qui au point de vue morphologique sont l'équivalent des cellules cancéreuses semblent être produites dans le col pendant au moins une période de la vie de plusieurs femmes chez qui on n'a jamais encore découvert des signes de cancer. Le diagnostic cytologique est rendu possible seulement parce que dans le cancer plusieurs de ces cellules apparaissent dans les frottis. Ces données laissent entendre que la déviation de la normale aboutissant au cancer s'établit par phases, et qu'elle n'atteint son plein épanouissement que chez un petit nombre d'individus.

SERUM TRYPSIN: A NEW DIAGNOSTIC TEST FOR PANCREATIC DISEASE

The diagnosis of pancreatic disease, especially chronic pancreatitis and carcinoma, is difficult and sometimes impossible. Determination of serum amylase and lipase is only of diagnostic value in acute inflammatory states, as elevated values are usually very transient.

The experience of Nardi and Lees (*New England J. Med.*, 258: 797, 1958) indicates that there is a significant elevation of serum trypsin in the presence of pancreatic disease. This elevation appears to be specific. A simple method for the quantitative analysis of circulating serum trypsin is presented, along with evidence of its reliability in clinical use in 16 patients with pancreatitis, in seven with carcinoma of the pancreas, and in a control group of 35.

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CERVICAL CURETTAGE AS A ROUTINE OFFICE PROCEDURE FOR THE DETECTION OF CARCINOMA OF THE UTERINE CERVIX

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IN CANADIAN WOMEN, the uterine cervix is the fourth most common site of origin of lethal cancer.[1] Results of treatment are generally agreed to be good when carcinoma is still confined to the uterine cervix.[2] It appears, therefore, that diagnosis at this stage should lower significantly the present considerable mortality from this disease. The planned, periodic, thorough examination of asymptomatic women obviously forms the basis of efforts to achieve this. Since carcinoma has been found repeatedly in the grossly healthy cervix and since it is frequently impossible with the naked eye to distinguish between chronic cervicitis, cervical erosion and early carcinoma, an adequate diagnostic technique should include not only a complete gynæcological history, speculum examination and bimanual pelvic examination, but also microscopical evaluation of cells or tissue from the cervix. While cone knife biopsy is indicated in suspicious cases, some simpler and less traumatic procedure that can be done in the office is required as a routine "screening" test.

The cytological examination of suitably stained smears of fluid from the posterior fornix or cervical canal has proved valuable in the detection of early cervical carcinoma.[3-5] However, practical difficulties in the establishment of special cytological laboratories frequently exist.[6] Another diagnostic aid that has been used with success is the microscopical examination of paraffin-embedded and sectioned tissue scraped from the cervix. Material for preparations of this sort can be obtained in the office, and sections can be made and examined as part of the daily routine in any laboratory of surgical pathology. This cervical scraping "surface biopsy" technique was suggested by Schiller[7] in 1928, but was little used at first. Of recent years Novak[8] and Hilliard[9] among others have employed it with good results. For this type of examination, Nolan and Budd[10] devised a curette having as its head a wedge-shaped spiral cup with a cutting edge, in order to obtain mucosa not only from the squamo-columnar junction, but also from higher in the endocervical canal.

We report our experience with the cervical scraping "surface biopsy" technique, using the instrument devised by Nolan and Budd, in 500 consecutive biopsies.

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MATERIAL AND METHODS

The 500 biopsies were obtained in the office from 417 patients encountered in the private gynæcological practice of one of us (A.H.) over a 5½-year period from May 1951 to October 1956. The majority of the patients were parous women with an endocervical discharge. The procedure was incorporated into the routine pelvic examination, without use of sedatives or local anæsthesia. Sponging of the cervix was avoided. With the earlier patients the cervix was steadied with a tenaculum, but later this was not found to be necessary, except in cases with very relaxed ligaments. The Nolan-Budd curette was introduced gently into the cervical canal, with rotation in a counterclockwise direction, until inserted as high in the canal as possible. Then, with moderate pressure of the edge of the instrument against the cervix, it was rotated fully in a clockwise direction one or two times. (Nolan[11] recommends that the handle of the curette be given a wide sweep, as in the Scanzoni manœuvre, to keep the blade firmly against the cervix, thus obtaining more material.) The tissue so obtained was wiped from the instrument's cup on to a piece of white scratch-pad paper, which was folded and at once placed in Bouin's fixative. The patients at most experienced a slight crampy pain. Adequate material was ensured only if sufficient pressure was exerted to give some discomfort and produce bleeding. The patients were reassured about the inevitable spotting and given a pad or tampon to wear. In every case bleeding stopped spontaneously.

On arrival at the laboratory the square of paper containing the specimen was unfolded and the coagulated material gently scraped from it with a scalpel blade. The material was then transferred to a square of filter paper, placed in a bouton and processed in an automatic tissue processor in the usual way. The specimen was removed from the paper after the second paraffin bath, embedded in fresh paraffin, and sectioned. The sections were stained with hæmatein, phloxine, and saffron.

Patients whose cervical scrapings were reported to be suspicious subsequently underwent a cone knife biopsy of the cervix, except in one case. Cone biopsy was also done in spite of a negative report on the scrapings if the clinical findings seemed to warrant it. Total hysterectomy, done for a variety of gynæcological conditions, permitted confirmation of the report on the scrapings in a further group of patients.

The cervical surface biopsies were examined by one of us (D.M.) while another (J.S.C.), usually unaware of the report on the scrapings, examined the cone biopsy and hysterectomy specimens.

RESULTS

Composition of samples.—The surface biopsies in 446 instances showed a various composition of cervical tissue fragments, cervical epithelial cells or both, frequently mixed with mucus and polymorphonuclear leukocytes. Fifty-four samples consisted of coagulated mucopurulent exudate and were adjudged inadequate.

In the biopsies containing tissue fragments, exocervical tissue was present alone in 108 samples and endocervical tissue alone was seen in 145 cases. In 95 instances both exocervical and endo-

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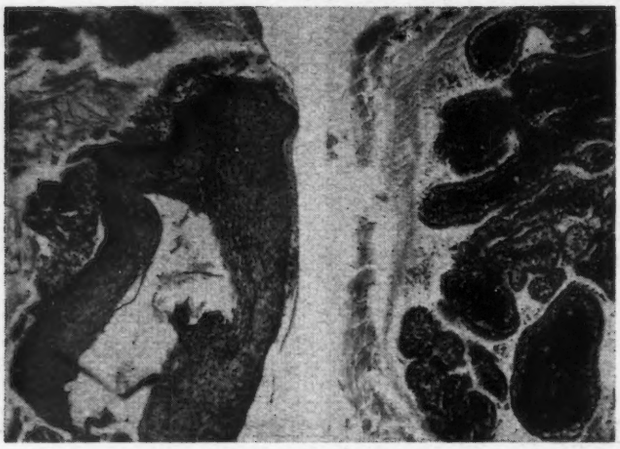

Fig. 1.—Cervical scrapings. On left, strips of stratified squamous epithelium. On right, polypoid endocervical fragments, covered by columnar epithelium and infiltrated with lymphocytes. Hæmatein, phloxine and saffron stain. × 55.

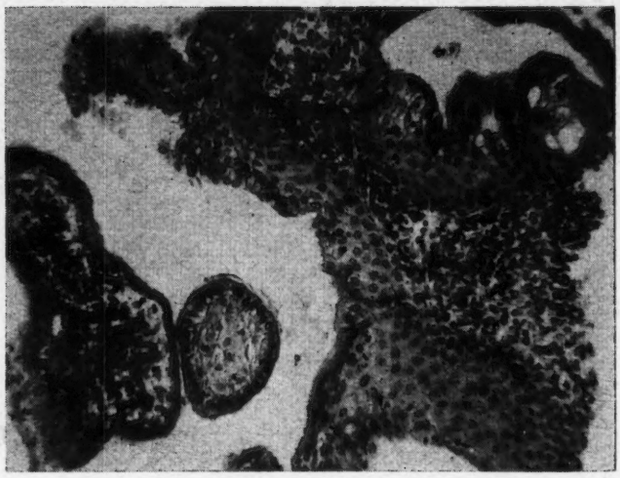

Fig. 2.—Cervical scrapings. Endocervical fragments showing orderly squamous metaplasia and lymphocytic infiltration. Hæmatein, phloxine and saffron stain. × 200.

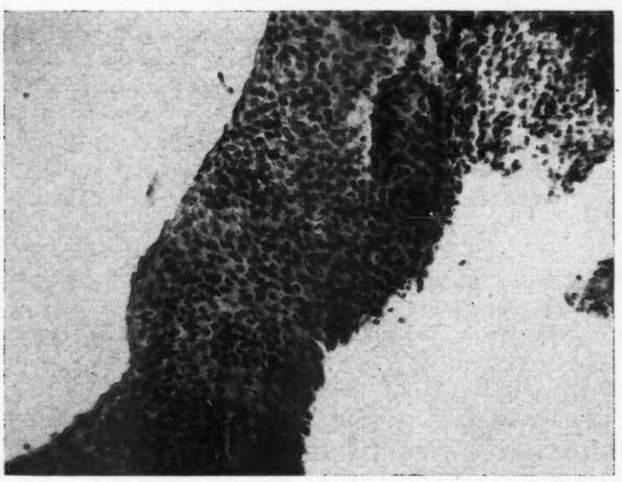

Fig. 3.—Cervical scrapings. A strip of epithelium showing loss of normal cell stratification throughout its thickness, and cell atypism. This was interpreted as "carcinoma *in situ*". Subsequent cervical biopsy was negative. Hæmatein, phloxine and saffron stain. × 200.

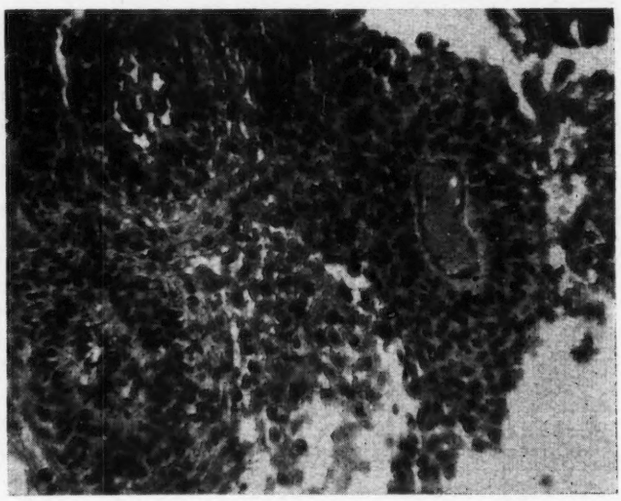

Fig. 4.—Cervical scrapings from a case not in this series. The loss of polarity of the epithelial cells and their extreme atypism permitted a diagnosis of carcinoma. Subsequent incisional biopsy revealed this to be invasive. Hæmatein, phloxine and saffron. × 200.

cervical elements were present. Endocervical tissue was usually represented by gland fragments or rounded structures having stromal cores covered by columnar epithelium. The latter evidently represented polypoid excrescences of endocervical lining. Squamous epithelium was often seen as fairly long epithelial strips, thought to represent strips of exocervical covering. Squamous epithelium was also present within endocervical gland lumina, replacing columnar epithelium to a greater or lesser extent and clearly representing metaplastic change. It was sometimes not possible to decide whether small fragments or rounded masses of squamous epithelium represented tissue from the portio vaginalis or endocervical foci of squamous metaplasia (Figs. 1 and 2).

Masses of epithelial cells seen in the scrapings were usually of the squamous type, although columnar cells from the endocervical mucosa were sometimes present. It was not possible to state whether squamous cells were derived from the epithelium of the portio vaginalis or from foci of endocervical squamous metaplasia, although when they occurred in the absence of endocervical elements the former view seemed more reasonable.

Pathological findings.—Of the 446 adequate cervical scrapings 438 were reported as negative (Table I). This group included 23 scrapings showing changes thought to represent simple epidermization of endocervical glands, a condition probably present in a larger number of specimens, for, as mentioned above, difficulty was encountered in distinguishing small fragment of exocervical epithelium from areas of endocervical squamous metaplasia. Also included in the negative group were 24 biopsies showing mild degrees of cervical

TABLE I.

Total number of "adequate" surface biopsies	446
Number of surface biopsies reported as "negative"	438
Number of patients subsequently submitted to cone biopsy	84
Number of patients subsequently submitted to hysterectomy for various benign gynæcological conditions	58
Number of biopsies rated as "false negative" on the basis of pathological examination of cone biopsy or hysterectomy specimen	2

dysplasia of the type that has been described under such terms as basal cell hyperactivity[12] and atypical hyperplasia.[13] The clinical findings in 84 patients in this negative group were deemed sufficient to warrant cone biopsy of the cervix to exclude carcinoma. Total hysterectomy was done in 58 other cases for a variety of gynæcological conditions. Pathological examination of this material confirmed the surface biopsy report, except in two cases. These two patients were reported pathologically to have carcinoma *in situ*. The surface biopsy reports had indicated the presence of cervical dysplasia but of a degree not considered to be alarming.

TABLE II.

Total number of "adequate" surface biopsies	446
Total number of patients with surface biopsies reported as "suspicious"	8
Number of patients with "suspicious" surface biopsies subsequently examined by cone biopsy	7
Report of cone biopsy:	
Early invasive carcinoma	1
Carcinoma *in situ*	2
Severe cervical dysplasia	3
Chronic cervicitis only	1

Cervical scrapings from 8 patients were considered to be "suspicious" (Table II). In 4 of these the microscopical appearance was such as to indicate the probability of carcinoma while in the other 4 the abnormal epithelium was somewhat less atypical. Of the 4 more suspicious cases subsequent biopsy revealed early invasive carcinoma in one case, carcinoma *in situ* in one case and cervical dysplasia deemed insufficient to warrant a diagnosis of carcinoma *in situ* in a third patient. The fourth case was negative on biopsy, but re-examination of the cervical scrapings (Fig. 3) did not alter the diagnosis and it was felt that the endocervical curettage had removed a carcinoma *in situ*. Of the 4 somewhat less suspicious cases, subsequent biopsy revealed carcinoma *in situ* in one case and cervical dysplasia in 2 cases; the fourth patient had left the country.

COMMENT

It is necessary to emphasize that the diagnosis of carcinoma *in situ* of the uterine cervix may vary with the pathologist examining the section.[14] We believe that we are conservative in the use of this term, and apply it only when normal stratification is lost throughout the thickness of the epithelium, with associated cellular atypism and loss of polarity. We would also like to stress that it has not been established that carcinoma *in situ* progresses invariably to invasive carcinoma[15] and that the biological relationship of cervical dysplasia to *in situ* and invasive cervical carcinoma has not been defined.[16] If one sets aside the uncertainties in the pathological diagnosis of cervical carcinoma *in situ* by whatever means, the method described in this paper would appear to be of value as a "screening" procedure suitable for office practice. It is usually not difficult to obtain the specimen once a little experience has been gained, if the curette is kept sharp. The specimen is easily handled in the pathological laboratory and the microscopic preparations can be thoroughly examined by the pathologist in a relatively short space of time. As in other screening procedures, false negative reports occur, so that a negative surface biopsy report does not allow one to dispense with cone biopsy in clinically suspicious cases.

SUMMARY AND CONCLUSIONS

Five hundred surface biopsies from 417 patients, obtained in the office by cervical curettage, included eight "suspicious" scrapings. Subsequent cone biopsy resulted in a pathological diagnosis of early invasive carcinoma in one case, carcinoma *in situ* in two cases and severe cervical dysplasia insufficient to warrant a diagnosis of carcinoma *in situ* in three cases. One case, negative on cone biopsy, was considered nevertheless to be carcinoma *in situ*. One case could not be followed up. Two "false negative" reports have been discovered, both cases of carcinoma *in situ*. The method would seem to be valuable as a "screening" test applicable to office practice, used as part of a procedure designed to detect carcinoma of the uterine cervix.

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RÉSUMÉ

Cet article traite des résultats obtenus au cabinet de consultation par curettage de l'exocol. Huit patientes d'une série de 417 chez qui on avait pratiqué un total de 500 biopsies de surface donnèrent un frottis suspect. L'évidement conoïde chez ces dernières permit de porter un diagnostic histologique de carcinome précoce invasif chez une malade, de carcinome *in situ* chez deux autres et de dysplasie cervicale avancée mais non encore néoplasique chez trois autres. Un autre cas fut considéré cancéreux en dépit d'une biopsie négative; la dernière malade ne se présenta pas pour l'examen de contrôle. La confrontation clinique ultérieure montra que deux rapports faussement négatifs furent donnés chez des cas de cancers intra-épithéliaux. La méthode offre un certain intérêt dans le dépistage au cabinet de consultation des lésions cancéreuses du col.

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LYMAN DUFF MEMORIAL LECTURE

TISSUE LESIONS IN HYPERSENSITIVITY*

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THE LATE GEORGE ADAMI,[1] while he was Professor of Pathology at McGill University, wrote the following in the preface to his monograph on inflammation, in the year 1906:

‡"Pathology has passed through its infancy, a long childhood, a stormy youth, and through a period of reaction. Now it may be said to have reached the age of maturity. There are those conscientious workers who maintain that it is immature. It is true many territories remain imperfectly explored, but there are others which have been worked over so abundantly and have yielded so vast a harvest of facts, that unless we proceed to marshal these facts into order, and to classify them in due relationship, one to another, the danger is imminent that the accumulation becomes a very chaos. So huge has become our subject that no one man can have an equal familiarity with the recent advances in neuropathology, hæmatology, teratology and antenatal pathology, immunity and the study of infection.

"This being so, it is urgent that some of those interested in medicine should give their time and energy not so much to the development of any one field, as to collecting and arranging the main data bearing upon the causes and development of morbid conditions."

These remarks are just as timely today as they were 51 years ago, and express clearly the objective in this presentation. In attempting to emulate Adami, I am not only following his precepts, but also taking some aspects of his subject, inflammation, as the principal theme.

Some of the tissue reactions in allergy, or hypersensitivity, have long been recognized as not being qualitatively different from other types of inflammation, but the nature of the injury causing the reaction is poorly understood despite extensive researches over the past 50 years. These investigations, beginning with the demonstration of antibodies and anaphylaxis, have progressed to an intensive study of changes in intercellular substance during the past 10 years. Volumes have been written about the pathology of connective tissue, but the relationship of these alterations to the general pathology of degenerations and inflammation is not, in my opinion, sufficiently stressed.

In selecting the injury and reaction caused by antigen-antibody mechanisms as the subject of this lecture, I am omitting any reference to the factors concerned in the development of hypersensitivity. One may define hypersensitivity as an altered state of reactivity of the body. The factors involved in this development and its nature are obscure and complex, and worthy of a fuller discussion than can be given at this time.

Many pathologists have attempted to define inflammation, and the most recent modification by Payling Wright[2] states: "Inflammation is the process by which cells and exudate accumulate in irritated tissues and tend to protect them from further injury." To many physicians inflammation and the general systemic reactions in inflammation mean infection. Such a confusion of cause and reaction is understandable, because the causes of inflammation, apart from bacterial infection, are only cursorily dealt with in most textbooks of pathology, while inflammation itself is usually discussed as a reaction to infection. Inflammation is, however, a local reaction of mesenchymal tissue, principally the blood and blood vessels. The definition does not include alterations in intercellular substance, which certainly contribute to the reaction, nor does it take into account the injury, which often plays a major part in determining the nature of the reaction of the mesenchymal tissue. It is my opinion that an appreciation of the nature of the inflammatory response must encompass an understanding of the character of the injury as well as the full scope of the changes in mesenchymal tissue in its broadest sense, including not only the blood and blood vessels but also the intercellular substance. Systemic reactions, such as fever, and the more subtle changes in the peripheral blood are also a part of inflammation and should be considered as well.

To try to fit hypersensitivity into this framework of injury and reaction may be premature, because the nature of the injury still escapes us and our knowledge of intercellular substance is still incomplete. However, a classification of hypersensitivity based on what we know at present of the conditions associated with injury may assist in our understanding.[3]

TABLE I.—HYPERSENSITIVITY

I.	Antibodies are not readily demonstrable.
	(Cellular or tuberculin hypersensitivity).
	Contact dermatitis.
	Bacterial infection.
II.	Antibodies are demonstrable and injury is related to antigen excess.
	(Anaphylactic hypersensitivity).
	Anaphylaxis.
	Serum sickness.
III	Antibodies are demonstrable and injury is related to antibody excess.
	Amyloid infiltration.
	Cryoglobulinæmia.

Cellular hypersensitivity, best exemplified by contact dermatitis, is characterized by cellular injury on direct contact with the antigen. The manifestations of the injury are delayed, usually some hours after exposure to the antigen.

Sensitization of epidermal cells may develop in susceptible individuals on exposure to simple

*First Lyman Duff Memorial Lecture, presented to the Medical Undergraduate Society, McGill University, Montreal, October 3, 1957.

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‡Abridged quotation.

chemicals, and even to elements such as chromium,[4, 5] through the adsorption by body proteins of the foreign substance and subsequent development of sensitivity to this protein modified by the adsorbed chemical. The injury is elicited by exposure to the chemical alone, not necessarily in combination with body protein. The nature of the injury is obscure, but it induces within the cell degenerative changes which may result in cell death or necrosis. An inflammatory reaction develops due to substances liberated by the injured cell; that is, the inflammation is a reaction to dead and autolyzing tissue.

More complex, but of the same order, is bacterial or tuberculin hypersensitivity. With a primary infection, sensitivity develops in all cells of the body, so that subsequent reinfection results in a hypersensitive injury and reaction. The injury causes cellular degeneration and necrosis, with an acute inflammatory response, including vascular dilatation and the formation of exudate. How much of this reaction is due to direct injury to vascular endothelium, and how much is a response to degenerating parenchymal cells, is unknown. The whole picture is complicated by the granulomatous inflammatory reaction to the tubercle bacillus and, as well, to the necrotic tissue. This more chronic inflammation is a response to insoluble, or slowly soluble, foreign material, including dead tissue. One sees it developing about the tubercle bacillus in the early stages of primary infection, before hypersensitivity develops.

The essential feature of cellular hypersensitivity is its association with vital functions of the cell, in that exposure to the antigen results in intracellular biochemical changes which may take some time to take effect, but most characteristically progress to cell death. A comparable type of injury is produced by some forms of irradiation, which may injure only the surface epithelium by inducing, we believe, intracellular ionization; this in turn leads to biochemical changes often progressing to cell necrosis, with an inflammatory reaction developing as a response to degenerative changes in epidermal cells. The analogy between cellular hypersensitivity and radiation injury may be carried further. Intravenous administration of the antigen in bacterial sensitivity may lead to death, but only after an interval of hours. Similarly, exposure to large doses of irradiation leads to symptoms and death only after a delay, and possibly for the same reasons. In localized injury of both types, that is, hypersensitivity and irradiation, the necrotic material which results may be relatively insoluble and provoke a surrounding granulomatous reaction.

I should like to mention at this point what is in my opinion an example of hypersensitivity of tuberculin or bacterial type characterized by caseous necrosis in the lungs, and induced by prolonged contact with an element. In the course of an experiment on the development of pneumoconiosis, rats were subjected to a heavy daily exposure of aluminium fumes. After a period of many months, focal and interstitial granulomatous lesions developed in the lungs, and these progressed over a further period of time to a coagulative necrosis and fibrosis, closely resembling that seen in tuberculosis and mycotic infections. My purpose in presenting this material is to illustrate that an element, aluminium, under certain conditions is capable of inducing hypersensitivity of apparently the same type as that usually associated with bacteria. If one compares this material with the contact dermatitis due to chromium, it demonstrates the variation in pathological picture resulting from different routes of administration and sensitization.

As stated earlier, the mechanisms underlying the development of cellular hypersensitivity are obscure, and one can only speculate about possible reasons why cellular hypersensitivity differs from anaphylactic hypersensitivity. It is possible that the relative insolubility of the antigen may be a factor, as it has been shown by Weil[6] that delayed anaphylactic shock may occur where sufficiently large amounts of antigen and antibody are not brought into sudden contact. Slow solubility of antigen would explain the delayed injury in cellular hypersensitivity, but not the differences in tissues sensitized. This in turn could be related to routes of administration and duration of exposure to the antigen. The slowness of development of injury may also, of course, be related to the relative quantity and availability of antibody.

Anaphylactic hypersensitivity may be defined as that type in which there are antibodies in the peripheral blood, demonstrable by various test-tube reactions such as precipitation, and also by passive transfer. Anaphylaxis, the Arthus phenomenon, serum sickness, and some forms of experimental nephritis and polyarteritis occur with this type. Some authors[3] do not include in this group sensitivity to pollens, as in asthma and hay fever, because antibodies are not demonstrable in peripheral blood by test-tube reactions. They are, however, demonstrable by passive transfer and the reaction elicited is of the same type[7] as the Arthus phenomenon, with local fixation of antigen and an immediate vascular inflammatory response.

If one considers first the nature of the injury in anaphylactic hypersensitivity, it has been postulated that the antibody is fixed to cells and that injury results when antigen reacts on the surface or within the cell.[8, 9] If antibody is present in the circulation in excess, or if the amount of antigen administered is insufficient, no injury occurs. The differences between anaphylaxis, Arthus phenomenon, and serum sickness are ascribed to different routes of administration of antigen and varying degrees of injury and reaction. This hypothesis has been thrown into question very recently by a brilliant series of experiments by Germuth,[10] who showed that anaphylaxis can be produced in a normal guinea-pig simply by the administration of a mixture of antigen and antibody, provided that

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the antigen is in excess and the antigen-antibody compound in solution. It has long been known that anaphylactic shock can only be produced in a sensitized animal by administration of antigen excess. If there is an excess of circulating antibody, shock does not develop. Germuth's experiments, which have not yet been confirmed by other workers, suggest that the antigen-antibody compound formed in the presence of excess antigen is capable of producing injury. The manner in which injury is produced remains obscure, and one does not know whether it is a direct effect of the immune body compound on cells or not. Experiments by Ungar[11, 12] suggest that combination of antigen and antibody releases protease from combination with anti-protease in the blood stream, and this enzyme and possibly others related to it injure tissue cells. The enzyme theory has not gained much support in recent years. Certainly, in acute anaphylactic shock, chemical changes in the blood include increase of histamine, heparin, acetylcholine, and other substances, and by classical definition the shock results in death in minutes.

Morphological changes associated with death in anaphylactic shock are minor, and may not be seen. However, in the more protracted and more localized injury of the Arthus phenomenon and in serum sickness, lesions involving vascular endothelium, basement membrane or cement substance of capillaries, intercellular substance, and smooth muscle are characteristically encountered. The basement membrane may become broadened and blurred, indeed may rupture. The endothelial cells swell, and thrombosis may result. In arteries, the injury is more complex, often with necrosis of smooth muscle of the vessel wall and marked changes in the intercellular substance. The injury to smooth muscle is directly due to the action of antigen-antibody compound in the presence of antigen excess, because it may be demonstrated *in vitro* with strips of smooth muscle. In man and in the experimental animal it is an acute degenerative change which may, but not always does, progress to necrosis. This injury is of the same order as the cellular type of hypersensitivity previously discussed. It differs in that it relates almost exclusively to vascular endothelium and smooth muscle, and the injury is an immediate one. The end result, necrosis, may however be just the same as in cellular hypersensitivity.

Let us consider next the intercellular substance and capillary basement membranes. I stated that the basement membrane may become thickened and frayed and may rupture. In arteries, fibrinoid necrosis or fibrinoid change often develops in the intercellular substance. This has been defined by Neumann as "swelling and homogenization, together with chemical changes in the intercellular substance of connective tissue". The nature of the change is still obscure. Certainly the morphological appearance results from coagulation and precipitation of protein and other substances, but the source of the material is disputed.[13] It is probable that some is derived from blood, because of the pouring out of fluid through injured vessel walls, and some from intercellular substance and basement membranes, and some from necrotic smooth mucle, in the case of arterial lesions. How much if any derives from altered collagen is doubtful, because collagen is a relatively inert fibrous protein, not readily attacked by enzymes. Although fibrinoid necrosis is so often associated with hypersensitive lesions that it has been considered specific by some authors,[14] it is not the only alteration in intercellular material. A mucoid change,[15] characterized by accumulation in the connective tissue of acid mucopolysaccharides, notably hyaluronic acid, also occurs. How much of this is due to direct injury, and how much is due to alterations in the blood and increased vascular permeability, is unknown. The changes in intercellular substance and connective tissue that may result from increased vascular permeability alone are exceedingly complex, and include increased glycolysis, alterations in pH and ion content, and accumulation of acid mucopolysaccharides. When one considers too the importance of adrenal corticoids and other hormones, and vitamins such as ascorbic acid, in the maintenance of the integrity of intercellular substance, it is understandable that we still have much to learn about the nature of injury and reaction in connective tissue.

None of the various types of injury given above is specific. Cellular necrosis may be caused by a variety of agents, such as chemical poisons and toxins and physical agents like irradiation and heat. Alterations in the intercellular material are likewise produced by many other agents. Fibrinoid change in arteries may be found in radiation injury, where it is probably due in part to altered permeability of basement membranes, and may in addition be due to direct injury of intercellular substance. In the base of peptic ulcers it is found, possibly as a combination of necrotic tissue and precipitated serum protein. Alteration in basement membranes of capillaries occurs in endocrine disturbances, such as myxœdema where, too, intercellular substance may become mucoid in character. One should not forget either the importance of changes in intercellular substance produced by some types of bacterial infection, notably that due to hæmolytic streptococcus. Here the injury is extensive, in the sense that tissue cells and vascular endothelium may both be injured by diffusible toxins and enzymes. The basement membranes and intercellular substance are doubly attacked by H substances liberated by injured cells, and by enzymes like hyaluronidase manufactured by the bacteria. Intercellular material becomes mucoid, more fluid, and profoundly altered in chemical composition.

Although none of the individual features of the anaphylactic type of injury is specific any more

than the response to that injury, we have come to recognize the combination of anatomical location of the lesions, the type of degenerative change, together with the character of the inflammatory reaction, as reasonably good evidence that hypersensitivity is the cause.

What are the reactions, then, to degeneration and necrosis of endothelium and smooth muscle, to mucoid degeneration and fibrinoid necrosis of intercellular substance? As stated before, the response to direct injury of endothelium is exudation of fluid and cells. Injury to smooth muscle will excite a similar vascular reaction, with production of a non-specific inflammatory exudate. The typical lesions of anaphylactic hypersensitivity, best observed in acute arteritis, may also be demonstrated in the glomerulus.

In discussing reaction to injury induced by anaphylactic hypersensitivity, I have stressed the acute inflammatory reaction. One may, however, encounter more chronic types of productive inflammation, related to the slow solubility of necrotic material, and to repair.

The stimulus to proliferation may be a primary effect of the irritant, that is, the antigen-antibody reaction. This is seen in experimental nephritis, where proliferation of endothelium of the glomeruli is a common feature. Proliferation of capillary endothelium is a common feature in many infections, and in some neoplasms of nervous origin as well. Whether in these instances it is due to a hypersensitivity mechanism or not, is unknown. Whether a similar effect on connective tissue obtains is not clear. Certainly there is proliferation of connective tissue whenever necrosis results. It is also possible that the accumulated macrophages, in the more chronic type of inflammatory response, may participate in laying down fibres. The increase in collagen that is seen in end-stage hypersensitive lesions may not be the result of cellular proliferation at all, but simply a product of progressive change in intercellular substance. It is commonly accepted, however, that connective tissue cells have an integral part to play in the laying down of intercellular fibres. In the lesions of experimental hypersensitivity I have not commonly observed scarring as an end result, and in fact have been struck more often by the absence of recognizable scars in animals that have survived acute serum sickness.

Amyloidosis.—In the broad classification of hypersensitivity given earlier, the last category included that type characterized by the production of antibody excess. The condition or lesion of amyloid infiltration may develop from precipitation of antibody with the polysaccharides of intercellular substance. Again, the mechanisms and causes of precipitation are obscure, and are not necessarily related to the blood level of circulating globulins. This precipitate, named amyloid by Virchow, has been familiar to pathologists for generations. Its association with long-standing infection has also been well recognized. The location of precipitation is not surprising when one considers amyloid as a manifestation of a hypersensitivity mechanism, related to antibody formation, and possibly too, related to interaction with antigen. It is deposited in intimate association with vascular endothelium. It is impossible to know whether the deposition is a response to injury of intercellular substance and basement membrane, or whether the deposition represents the injury. If the latter is the case, the injury is of bland type, exciting no demonstrable inflammatory response in the usual sense. It produces further changes indirectly by interposing a barrier between the capillary wall and the parenchymal cell. Such a barrier has serious functional effects in the kidney, resulting in renal insufficiency.

Akin to amyloid is the hyaline and para-amyloid which is found in the glomerulus in glomerulonephritis and other conditions. This material is regarded by Teilum[16] and Oberling[17] as similar in nature to amyloid. It is now recognized that amyloid, although basically protein in combination with mucopolysaccharides, is of variable composition and does not always give the classical staining reactions.[18] In a study of the natural history of experimental glomerulonephritis in the rabbit,[19] only one animal died within a month of the shocking dose of foreign serum, with infiltrations in the glomerulus resembling secondary amyloid deposit in man, but not giving the usual staining reactions.

Although amyloidosis is recognized as a consequence of prolonged antigenic stimulation mediated through development of antibody excess, it is not a specific type of lesion at all, but may be a result of formation of excess globulin from other causes. For example, the amyloid found with multiple myeloma is related to proliferation of plasma cells. The distribution of the deposit is not the same as in secondary amyloidosis, in that amyloid infiltrates the mesenchymal tissues, such as muscle, bone, and connective tissue rather than vascular endothelium of liver and kidney. Again, no correlation with blood level of circulating globulins is found. It is possible that the globulins produced by the plasma cells of multiple myeloma are abnormal, and differ from antibody globulins, but again, the cause of precipitation remains obscure, just as the site of precipitation is unexplained.

Closely allied to amyloidosis, but with different manifestations, is cryoglobulinæmia, a condition characterized by the presence in peripheral blood of gamma globulins which precipitate with cold and redissolve on warming.[20] Vascular occlusion may occur, and result in necrosis and gangrene, but other changes, including reddening of skin and urticaria, suggest a reaction to injury of vascular endothelium. Again, however, the mechanism of the injury is obscure. The association of cryoglobulinæmia with periarteritis nodosa, chronic

nephritis, and kala-azar, is presumptive evidence that it is the product of an immune mechanism. This is supported by the electrophoretic pattern, which shows cryoglobulins migrating with the gamma globulins.[21] However, just as with amyloidosis, cryoglobulins may be found in multiple myeloma and chronic lymphatic leukæmia. It is suggested that these proteins are abnormal and of a different order from those related to amyloid infiltration.

In the foregoing account of tissue injury and reaction, all discussion of systemic changes which might be related to the development of the lesions has been purposely left out. As stated in the introduction, the field of hypersensitivity embraces the whole of medicine and all its disciplines, and to embark upon the physiological disturbances, such as those of the endocrines and the blood, is beyond the scope of this paper. I would like to suggest, however, that some of the generalized symptoms associated with hypersensitive lesions and injuries, such as fever and toxæmia, could be due to absorption of products of cell degeneration.

I have pointed out that the tissue lesions in hypersensitivity fit into the broad group of degenerations and reactions of general pathology, and are not in any way specific. Lyman Duff,[22] in his lecture to the Royal College on collagen diseases, pointed out that morphological resemblance of lesions in different disease entities does not justify the assumption of a common etiology.

Clinical and experimental evidence, however, has proven quite conclusively that cellular hypersensitivity is of major importance in tuberculosis,[7] and that anaphylactic hypersensitivity is the major pathogenetic mechanism in serum sickness, periarteritis nodosa, and allergic diseases such as asthma.[23] The evidence that immune reactions are altered in diseases such as rheumatic fever, rheumatoid arthritis, acute disseminated lupus erythematosus, and scleroderma, together with the similarity of many of the tissue lesions to those in proven hypersensitive disease, certainly lends support to the belief that they too may be caused by hypersensitivity. However, we know so little of the pathogenesis of the hypersensitive state that the basic etiology may lie in currently unknown factors which determine whether or not a given individual shall or shall not become hypersensitive.

This biologic state of altered reactivity may be induced by different etiological mechanisms, but once established may follow a limited pattern of manifestation. One cannot, in my opinion, improve upon the concept advanced by Lyman Duff[22] in talking about collagen disease:

"Accordingly, we can assume a similarity of pathogenesis among the various collagen diseases only in the last of the sequence of pathogenetic events that occur within the tissues themselves."

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RÉSUMÉ

Il est reconnu depuis longtemps que certaines réactions tissulaires en allergie ou hypersensibilité ne sont qualitativement différentes en rien de celles qu'on rencontre dans d'autres genres d'inflammation, mais en dépit de recherches intenses menées depuis 50 ans, la nature précise de ces lésions demeure obscure. Aux yeux de plusieurs l'inflammation et ses réactions systémiques n'évoquent que l'infection. D'après Payling Wright l'inflammation ne serait qu'un processus par lequel les cellules et l'exsudat s'accumulent dans un tissu irrité à fin de le protéger contre d'autres lésions plus graves. L'application de cette définition à l'allergie peut être spécieuse puisque la cause du processus ainsi que la nature exacte de la substance intercellulaire nous échappent encore.

La sensibilisation cellulaire comme on la voit dans la dermatite de contact est caractérisée par une lésion cellulaire au contact immédiat de l'antigène. La cellule meurt et la réaction inflammatoire qui suit est déclenchée par la libération des produits de décomposition des tissus morts et nécrosés. Dans le même ordre d'idée se range l'hypersensibilité bactérienne ou tuberculinique. La part de cette réaction qui échoit aux lésions endothéliales vasculaires reste encore indéterminée. Le trait essentiel de la sensibilisation cellulaire réside en sa relation intime aux fonctions vitales de la cellule; les altérations biochimiques qui s'amorcent au contact de l'antigène mènent à sa destruction. Des lésions comparables résultent de l'irradiation des tissus même si elle n'atteint que l'épithélium de surface. Les modifications du phénomène seraient reliées entre autres au degré de solubilité de l'antigène ainsi qu'à la quantité relative d'anticorps disponible.

L'hypersensibilité anaphylactique (phénomène d'Arthus, maladie du sérum, certaines formes expérimentales de néphrites et de polyartérites) implique la présence préalable d'anticorps dans le sang périphérique. Les données les plus récentes sur le sujet semblent indiquer qu'un excès d'antigène est essentiel à la production de l'anaphylaxie; on peut la déclencher par injection d'un mélange anticorps-antigènes pourvu que ceux-ci prédominent. Certains auteurs croient à une libération de protéase dans l'union d'anticorps et d'antigènes; cette enzyme serait à l'origine des lésions. Au point de vue morphologique la membrane de base s'épaissit et perd de sa netteté; elle peut même se rompre; les cellules endothéliales se gonflent souvent au point de causer une thrombose du vaisseau. On observe aussi une nécrose des muscles lisses des artères ainsi qu'une nécrose fibrinoïde de la substance intercellulaire. L'apparence morphologique provient évidemment de la coagulation et de la précipitation de protéïnes et d'autres substances, mais la provenance de ces produits reste encore indéterminée. On

note aussi dans le tissu conjonctif une accumulation de mucopolysaccharides acides comme par exemple l'acide hyaluronique. Aucune de ces lésions n'est spécifique et plusieurs peuvent se retrouver dans un grand nombre d'états morbides; cependant si l'on considère la situation anatomique, le genre de dégénérescence ainsi que le caractère de la réaction inflammatoire on peut incriminer l'hypersensibilité avec raisonnablement de certitude.

Lorsqu'il y a précipitation d'anticorps en présence de polysaccharides de la substance intercellulaire le résultat, décrit jadis par Virchow, se traduit par la dégénerescence amyloïde. Sa déposition en relation avec l'endothélium vasculaire s'explique si l'on considère son origine; on ne sait cependant pas encore si la dégénérescence est le résultat de l'atteinte à la substance intercellulaire ou si elle représente l'atteinte même. L'effet de cette déposition est d'isoler les tissus adjacents au vaisseau, et de nuire ainsi à son irrigation sanguine. Les dégénérescences hyaline et paraamyloïde sont de nature connexe. La cryoglobulinémie se rapproche de la dégénérescence amyloïde sans toutefois s'identifier complètement à elle. Cette aberration consiste en la présence dans le sang périphérique de globulines gamma qui précipitent au froid et se redissolvent au chaud. Dans leur forme insoluble elles entraînent certaines perturbations hémodynamiques occlusives et causent de la nécrose et de la gangrène. Sa parenté avec la périartérite noueuse, la néphrite chronique et le kala-azar laisse supposer un mécanisme d'immunité. On doit se garder ici comme ailleurs d'attribuer une étiologie commune aux lésions morphologiquement semblables.

ASEPTIC MENINGITIS IN MANITOBA, 1957*

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VIRUS INFECTION of the central nervous system with paralysis is almost always due to poliomyelitis, whereas those virus infections with manifestations of encephalitis or meningitis are usually associated with infectious diseases such as measles or mumps; occasional outbreaks of encephalitis due to the arthropod-borne viruses occur, e.g., Western equine encephalitis.

In addition, a rather large group of benign central nervous system infections are seen, to which the term "aseptic meningitis" has been applied. Despite the inadequacy of this term, it has become widely adopted to describe a fairly well defined clinical entity. The clinical syndrome of aseptic meningitis refers to a febrile illness, usually in a child (occasionally with a "saddle-back" type of fever reaction), associated with headache, malaise, leg aches, neck stiffness, and pleocytosis in the spinal fluid with increased protein and normal or elevated sugar values. The disease is rarely associated with weakness or paralysis, but in some outbreaks, especially in England, a macular eruption has been described in about 25% of cases. The disease runs a course of about 5-10 days and there are no sequelæ. The Coxsackie B group of viruses were first isolated from patients with aseptic meningitis in 1947;[1] the Coxsackie A viruses have also been shown to produce this syndrome but much less frequently.[2] The importance of the ECHO viruses in etiology of aseptic meningitis has only recently been established. Some recent reports are summarized in Table I.

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CLINICAL DISCUSSION

Twenty patients with aseptic meningitis were admitted to the Winnipeg Children's Hospital between July 22, 1957 and September 1, 1957. Fourteen of these were male and six female. The cases were equally distributed by age (Fig. 1) but the more severe cases occurred in the infant group. Three cases occurred in infants less than one year of age, two of whom had convulsions during the course of their illness.

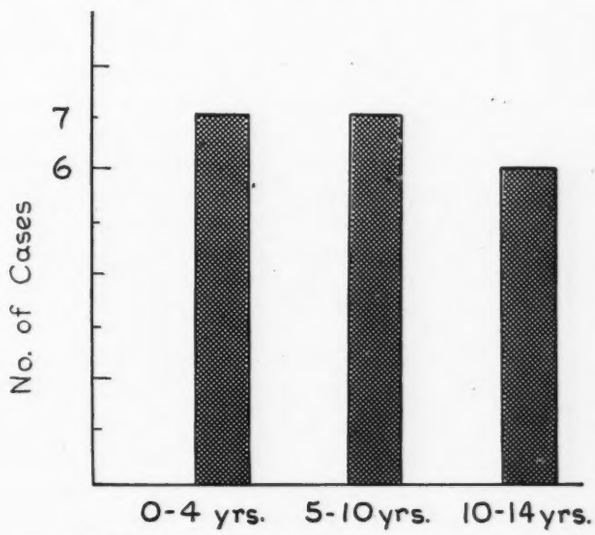

FIG. 1.—Age incidence of aseptic meningitis, Winnipeg Children's Hospital, 1957.

In 65% of the cases, the illness lasted 5-10 days. One patient had a shorter illness, and six had a more prolonged course; in one case, in a girl of 13 years, the duration of illness was 18 days. Three patients had a biphasic or "saddle-back" type of illness, the period of "well-being" lasting 7-10 days. Two cases of special interest were in patients whose illness lasted more than 10 days.

CASE 1.—Age 3 months; severely ill on admission; repeated convulsions. Spinal fluid on admission showed 95 leukocytes per c.mm., 74% polymorphonuclears, 26% lymphocytes, protein 25 mg. %, sugar 45 mg. %. Two

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TABLE I.—ASEPTIC MENINGITIS AND ECHO VIRUSES
REVIEW OF LITERATURE

Author	*Reference*	*No. of cases*	*Geography*	*Virus isolated*	*Age*	*Year of study*	*Clinical features*
Kibrick *et al.*	Ann. New York Acad. Sc., 67: 311, 1957.	40	Massachusetts	ECHO 6	7–17	1951–54	Clinically mild poliomyelitis. Transient muscle weakness.
Meyer *et al.*	Ann. New York Acad. Sc., 67: 332, 1957.	13	Army Camp U.S.A.	ECHO 6 or related	Military Personnel	1954–57	Aseptic meningitis, non-paralytic
Davis and Melnick	Proc. Soc. Exper. Biol. & Med., 92: 839, 1956.	69	Connecticut	41% polio, 23% Coxsackie, 36% ECHO (25 cases—21 type 6)		1955	Non-paralytic illness. Aseptic meninggitis.
Davis and Melnick	Proc. Soc. Exper. Biol. & Med., 92: 839, 1956.	3	Rhode Island	ECHO 6		1954	Aseptic meningitis.
Karzon *et al.*	J. A. M. A., 162: 1298, 1956.	24	Holland, N.Y. Total pop. 500	7 cases ECHO 6, plus 7 cases ECHO 6 in adjoining communities.	Children	July, 1955	Aseptic meningitis.
Boissard	Lancet, 1: 500, 1957.		Various parts of England	ECHO 9		1956	Aseptic meningitis.
Tyrrell and Snell	Lancet, 2: 1028, 1956.		Sheffield	ECHO 6	10 years	Sept., 1956	Many had a macular rash.
Garnett	Lancet, 1: 500, 1957.	130	East Suffolk, England	ECHO 9 (C.S.F. of 5 patients. Stools of 6 patients. Throat of 4 patients.)	All ages	1955–56	Aseptic meningitis, plus macular rash in 25%.
Rotem	Lancet, 1: 502, 1957.	100	Leicester, England	ECHO 9 in "several" patients		July-Nov. 1956	Aseptic meningitis plus macular rash.
Winkelstein *et al.*	Am. J. Pub. Health, 47: 741, 1957.	156	Erie County, N.Y.	ECHO 6 in 106 patients (8/11 C.S.F. isolations).		1957	Aseptic meningitis.
Wilt, Medovy, Besant and Stackiw		20	Children's Hospital, Winnipeg, Canada	ECHO 6 in 7 cases; ECHO 9 in 1 case.		1957	Aseptic meningitis; no rash.
Laforest *et al.*	Canad. M. A. J., 77: 1, 1957.	115	Toronto and vicinity	58 isolations in children from fæces; 15 isolations from C.S.F., 13 strains were ECHO 9.		1956	Aseptic meningitis.
Faulkner, MacLeod and van Rooyen	Canad. M. A. J., 77: 439, 1957.	7	Halifax	3 isolations from fæces; 1 isolation from C.S.F. ECHO 9.	All ages	1957	Aseptic meningitis.

days later the spinal fluid cell count had risen to 250 cells per c.mm. with 78% polymorphonuclears and 22% lymphocytes, sugar and protein content normal. Eight days later, the spinal fluid was normal. The infants recovered without sequelæ.

CASE 2.—A girl 13 years of age. Onset of illness with nuchal rigidity, fever and headache. Spinal fluid normal on admission. Three days later, the spinal fluid contained 560 cells per c.mm.; 66% were polymorphonuclears and 22% were lymphocytes.

CLINICAL COURSE

The frequency of symptoms is indicated in Fig. 2. All patients had fever and nearly all had headache and stiff neck. Vomiting occurred in half the patients; convulsions were infrequent and occurred mainly in the infant group; no patients were seen with rash. In general, except for the infants, the illness was not too severe. Headache and fever caused considerable discomfort and little

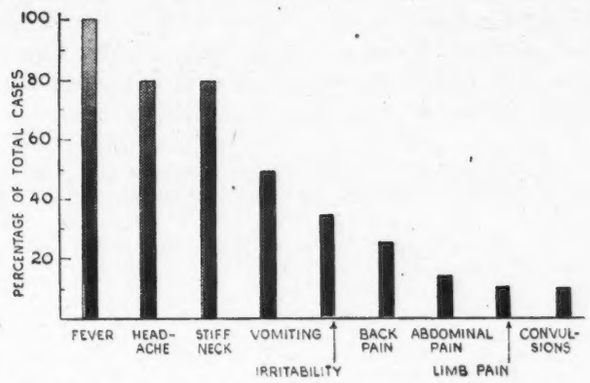

Fig. 2.—Symptoms in cases of aseptic meningitis, Winnipeg Children's Hospital.

inclination to eat. The sensorium was clear and there was no unusual lethargy or irritability. Fever and headache subsided in a few days and there were no sequelæ.

The combination of an acute onset of fever and headache, with vomiting in most cases, in a child who did not otherwise appear too ill and the presence of signs of meningeal irritation led to the presumptive diagnosis of non-bacterial meningitis.

LABORATORY RESULTS

The spinal fluid findings are shown in Fig. 3. The spinal fluid showed a pleocytosis of 20-300 cells per c.mm. in 15 patients; the cells were initially polymorphonuclear with a transition to lymphocytes in the later stages. The protein in the spinal fluid was not markedly elevated, varying from 0 to 40 mg. per 100 ml. in 12 patients. Bacteriological cultures of spinal fluid were negative. Sugar content was also normal.

An attempt was made to obtain fæces, cerebrospinal fluid, and paired blood samples (acute and convalescent) from each patient for virus examination; complete collections were not made from all, as is shown in Table II. In 12 of the 20 patients the infection was identified as viral in etiology: eight by isolation of virus and four by demonstrating a rise in antibodies to the ECHO virus during the course of the disease. Five of the isolates were identified as ECHO type 6 (one from

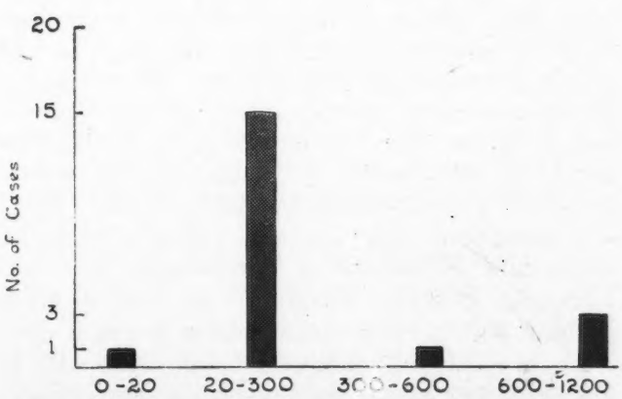

Fig. 3.—Spinal fluid cell count in cases of aseptic meningitis, Winnipeg Children's Hospital.

TABLE II.—ASEPTIC MENINGITIS: POSITIVE RESULTS IN 12/20 PATIENTS (WINNIPEG CHILDREN'S HOSPITAL, 1957)

Patient	*Specimen*	*Virus isolation*	*Serology*
V.P.	Fæces, C.S.F., blood	ECHO 6 (fæces)	1:10 to 1:160 (ECHO 6)
K.F.	Fæces, blood	Not identified	No rise in titre (ECHO 6)
L.L.	Fæces, C.S.F., blood	ECHO 6 (fæces)	1:5 to 1:80 (ECHO 6)
A.	Fæces, blood	ECHO 6 (fæces)	1:20 to 1:320 (ECHO 6)
K.F.	C.S.F.	ECHO 6	
M.F.	Fæces, blood	ECHO 6 (fæces)	1:10 to 1:80 (ECHO 6)
K.E.	Fæces, throat swab	Coxsackie A (fæces)	
M.H.	Blood		1:10 to 1:40 (ECHO 6)
K.O.	C.S.F., blood	Negative (C.S.F.)	1:160 to 1:160 (ECHO 6)
K.S.	Blood		1:5 to 1:40 (ECHO 6)
T.P.	Fæces	Coxsackie A	
S.J.	Blood		1:5 to 1:80 (ECHO 9)

spinal fluid), two of the isolates as Coxsackie group A, and one as ECHO type 9. Four of the patients from whom an ECHO type 6 virus was isolated also showed an increase in antibodies to this virus during the course of the infection.

Table III shows the results obtained in other parts of the community from 17 patients classified clinically as having aseptic meningitis. Five of the viruses isolated were identified as poliomyelitis virus (4 of type 1 and 1 of type 2), five were identified as ECHO 6, three were identified as ECHO type 9, one as Coxsackie group B type 3, and one as Coxsackie group A. In addition, one patient showed an antibody rise to ECHO type 9 virus but no virus was recovered. The patient from whom the ECHO 9 virus was recovered had a rash and was diagnosed clinically as having measles encephalitis; two other members of the family had the same infection.

DISCUSSION

The patients studied at the Children's Hospital represent a sampling of infections of this type which occurred in the city and province throughout the late summer of 1957. Some of these patients were admitted to other hospitals, some were treated at home, and no doubt some did not have

TABLE III.—ASEPTIC MENINGITIS: POSITIVE RESULTS IN 17 OTHER PATIENTS, 1957

Patient	*Specimen*	*Virus isolation*	*Serology*
R.K.	Fæces	Type 1 polio	
B.F.	Fæces	Type 1 polio	
R.D.	Fæces	Type 2 polio	
L.P.	Fæces	Type 1 polio	
J.T.	Fæces	Type 1 polio	
F.H.	Fæces	ECHO 6	
M.Z.	C.S.F.	ECHO 6	
J.G.	Fæces	ECHO 6	
G.S.	Fæces	Not identified	
F.C.	C.S.F.	ECHO 9	
D.T.	Fæces	ECHO 6	
K.B.	Fæces	ECHO 9	
A.B.	Blood		1:5 to 1:160 (ECHO 9)
G.G.	Fæces	Coxsackie B 3	
C.R.	Fæces, C.S.F., blood	ECHO 6 (C.S.F., fæces)	1:5 to 1:20 (ECHO 6)
K.M.	Fæces	Coxsackie A	
Y.W.	Throat	ECHO 9	

a physician in attendance. Since the reporting of benign encephalitis is not too reliable, it is impossible to determine the total number of infections of this type that occurred; it is probable that the 20 patients reported here represent the majority of the most severe infections.

The initial clinical diagnosis on the hospital group of patients was aseptic meningitis; the etiological possibilities included poliomyelitis, Coxsackie virus infection, and ECHO virus infection. It is impossible, however, to make an etiological diagnosis from the clinical picture. In former years, the more severe infections would have been classified as nonparalytic poliomyelitis.

CONCLUSION

An outbreak of aseptic meningitis which occurred in the province of Manitoba in the summer of 1957 is described.

Twelve of the 20 cases investigated at the Children's Hospital were identified as virus infections; eight were due to ECHO type 6 virus, two to Coxsackie group A, and one to ECHO type 9 virus, while one was unidentified.

Seventeen cases of aseptic meningitis outside the Children's Hospital were also identified as virus infections in five cases with poliomyelitis, five with ECHO type 6, four with ECHO type 9, one with Coxsackie group B, and one with Coxsackie group A virus; one was unidentified.

Acknowledgments are due to the clinicians at the Winnipeg Children's Hospital for their co-operation in these studies.

Virus investigations were carried out under General Public Health Grant No. 606-11-12.

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RÉSUMÉ

Cet article comprend la description d'une épidémie de méningite aseptique qui atteignit la province du Manitoba vers la fin de l'été 1957. On reconnut une infection à virus chez douze des vingt cas chez qui on rechercha l'étiologie. Huit relevaient du genre ECHO type 6, deux du genre Coxsackie groupe A, un du genre ECHO type 9, alors qu'un autre virus ne put être identifié. Dix-huit autres cas de méningite aseptique non admis à l'Hôpital des enfants furent également reconnus comme étant d'origine virale. Cinq d'entre eux relevaient de la poliomyélite, cinq du virus ECHO type 6, quatre du même virus, mais de type 9, un du Coxsackie groupe B, un autre du Coxsackie groupe A, alors que le dernier resta non identifié.

THE VALUE OF ELECTRODIAGNOSIS IN CLINICAL MEDICINE*

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DURING the last 15 years increasing interest has been shown in electrical methods of diagnosis and prognosis in lesions of the lower motor neurone. Since the war much work has been done on both sides of the Atlantic in this field. The developments in radar contributed much to the rapid advances in the design and accuracy of electronic stimulators and electromyographs.

Many different methods and techniques have been used to supplement clinical appraisal of the state of the lower motor neurone. There is today, however, as near general agreement as there is likely to be about the methods of choice that have proved their worth. This, therefore, seems an appropriate time to review their rationale, indications and place in clinical medicine.

Two traditional methods in common use ten years ago have failed to survive. The polar formula survives only in textbooks of neurology; no-one who actually performs electrodiagnostic investigations would ever consider using it now.

Similarly, the faradic-galvanic test should never be used, both because it is liable to give a misleading idea of the state of the lower motor neurone, and because it has been superseded by more accurate tests which are also easier and quicker to perform. The rationale of the faradic-galvanic test is conventionally that a denervated muscle responds sluggishly to a long duration impulse, or the output of a galvanic battery, and does not respond to a short duration current or the output of a faradic coil. It is frequently found that a recovering muscle shows a clinical contraction before it responds to faradism. Moreover, a high proportion of denervated muscles will respond to a current of short duration, provided sufficient output is given. The old faradic coils hardly ever provided output above 120 volts, but the modern electronic stimulators give outputs of 200 volts.

Furthermore, the modern voltage controlled therapeutic stimulator is comfortable and well tolerated. Patients, therefore, can tolerate high outputs, and a denervated muscle is much more likely to respond to a short pulse duration with an electronic stimulator than with the output of a conventional faradic battery.

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*This paper is based on a paper read at the Fifth Annual Meeting of the Canadian Association of Physical Medicine and Rehabilitation, Toronto, Ont., June 21 and 22, 1957.

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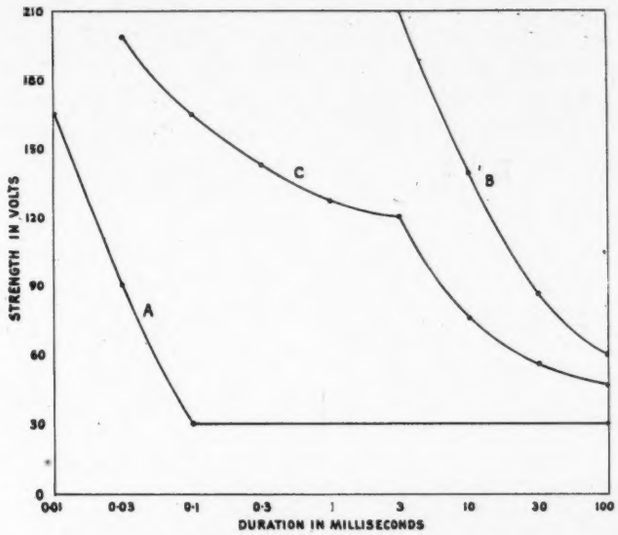

Fig. 1.—Strength duration curves of normal (A), denervated (B), and partially innervated (C) muscles.

If a positive response to a short duration current is interpreted as meaning that some nerve fibres are intact, the test will be gravely misleading. The nature of the test is such that it is incapable of fine gradations—it is an all-or-none test, and it does not provide evidence of early degeneration or allow comparative estimates of the progress of regeneration or degeneration.

Unfortunately physiotherapists still carry out these tests, and doctors with no experience of modern methods of electrodiagnosis base decisions on their results. It must be stressed that there is no longer any place for the use of the faradic-galvanic test. The two main methods in use today are the strength duration curve and electromyography.

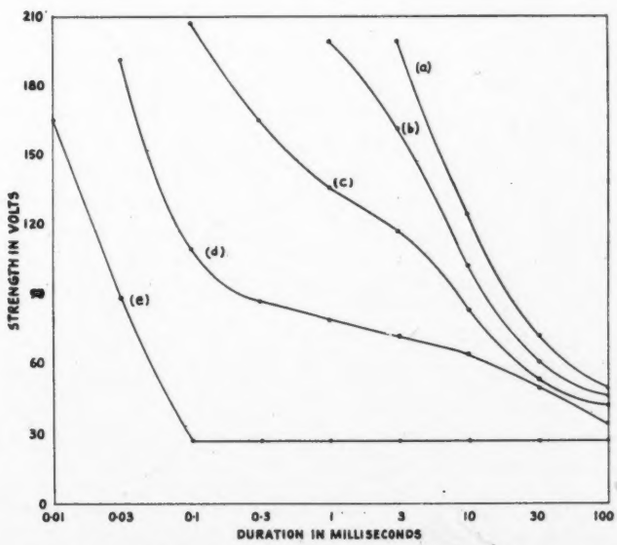

Fig. 2.—Serial strength duration curves on the abductor pollicis brevis in a patient with a recovering median nerve lesion sutured at the wrist: (a) Denervated curve eight weeks after suture. (b) Slight kink detectable—the first indication of reinnervation. This curve was taken four months after suture, voluntary movement was detected 5 weeks later. (c) Six months after suture—obvious double curve of partial innervation. (d) Eight months after suture. (e) A year after suture. The curve is now normal.

STRENGTH DURATION CURVE

In this method the relation of strength of current to produce minimal detectable contraction in the muscle with its duration, is measured and a curve plotted.

A long duration impulse (100 milliseconds) is first used and the minimal current (measured in volts or milliamperes) required to cause just perceptible contraction noted. This is by definition the rheobase. The duration is made progressively shorter (30 ms., 10 ms., 3 ms., 1 ms., 0.3 ms., 0.1 ms., 0.03 ms., 0.01 ms.) and the amount of current required to produce minimal contraction measured at each duration. Thus the strength duration (S.D.) curve is obtained.

When the muscle is normally innervated, the current stimulates the small intramuscular nerve fibres and thus the characteristic response of nerve is obtained (Fig. 1A). When the muscle is totally denervated, the current stimulates the muscle direct and thus the characteristic response of muscle is obtained (Fig. 1B). When the muscle is partially innervated a double curve results, containing elements of both nerve and muscle response (Fig. 1C). The shape of this double curve is an accurate guide to the amount of innervation (or denervation) present. The curve provides an expression of the ratio of innervated to denervated fibres.

A slight 'kink' in a curve that has previously been typical of denervation is the first sign of reinnervation and precedes clinical evidence by as much as 6-8 weeks.

The three features looked for are:

1. The appearance of kinks, which gradually widen out.
2. The shift of the curve to the left.
3. The fall in slope.

The denervated curve is gradually being transformed into the normal curve (Fig. 2).

It must be stressed that if the technique used is careful, slight changes in the normal curve are significant of early denervation, and conversely, slight changes in the denervated shape are significant of early regeneration. One of the useful features of the test is its extreme accuracy.

Inspection of the normal and denervated curves (Fig. 1) shows that these two curves are essentially the same in shape; the responses of nerve and muscle are thus of similar nature. The point at 100 ms. is by definition the rheobase, and so prolongation of the muscle curve to the right must make the curve horizontal, thus giving it the same shape as that of nerve. This is to be expected from two tissues whose activation is essentially the same—namely, membrane depolarization. The difference is a shift of the curve to the right—indicating a difference in time relationship, muscle being less excitable than nerve.

Two points on the curve have been widely used as indices of the state of the lower motor neurone. These are the rheobase and chronaxia. Rheobase,

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the minimal amount of current passing for infinite duration required to cause just perceptible contraction, is a measure of the threshold of excitability of a tissue. Whilst it is true that with denervation the rheobase of a muscle does generally drop, and with regeneration the rheobase often rises, these signs are neither consistent nor early enough to be used with confidence. In the author's series of 200 peripheral nerve injuries followed over a period of three years, the rheobase remained much the same in denervation and reinnervation in nearly half the cases. A sudden rise in rheobase may be significant but lack of it does not exclude the presence of reinnervation.

Nerve conduction testing must always be carried out before any other electrical examination. There are three main uses of nerve conduction tests.

First, it will reveal anomalies of innervation. One in five patients has an anomaly of innervation of some sort in the hand. One in six of all patients with median nerve palsies seen by the author has had the ulnar nerve supplying the opponens. Stimulation of the main nerves of the limb at convenient points will readily demonstrate this, and save confusion between a partial lesion and an anomaly of innervation.

Secondly, it will reveal the site of a conduction block in neurapraxia, and make further tests unnecessary. This is particularly useful in such lesions as radial nerve palsies and facial nerve paralysis.

Thirdly, it allows a general picture of the extent of damage or improvement without individual testing of many muscles. This is particularly helpful, for example, in brachial plexus palsies.

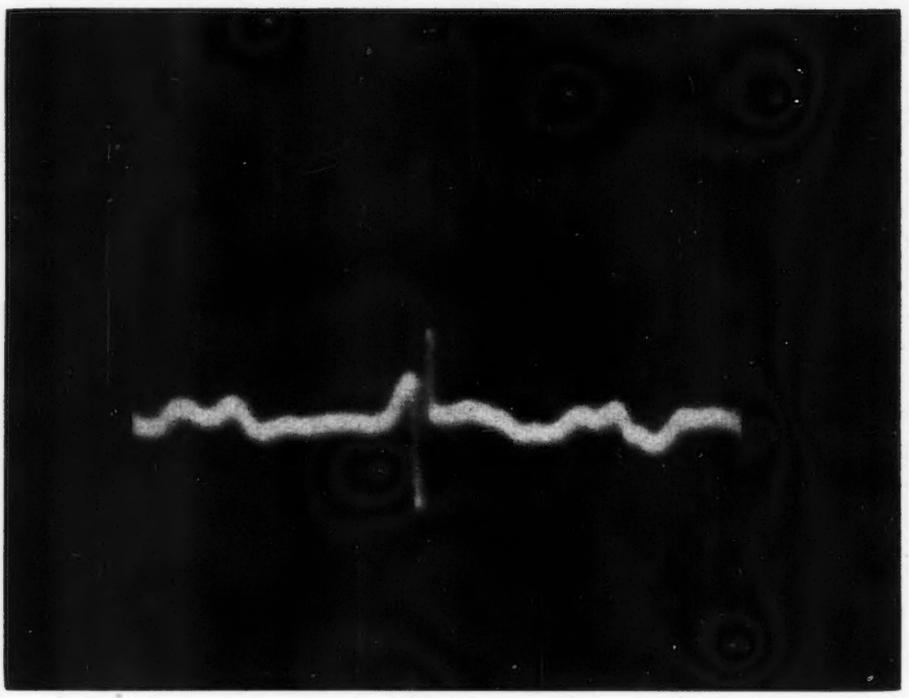

Fig. 3.—Fibrillation potential.

Chronaxia, the length of time for which a current of twice the rheobase must pass for contraction to occur, is the other index in common use. This is determined from the strength duration curve by finding where the value of twice the rheobase on the curve cuts the time base. It used to be found by using elaborate machines called chronaximeters. It is claimed that a rise in chronaxia indicates degeneration and a fall regeneration.

Certainly the chronaxia of normal muscle is short and denervated muscle long, but in advanced regeneration it may well still be long and in early denervation still short. There are unfortunately no intermediate values of chronaxia; the value is either long or short.

The curve with practice takes two or three minutes only to plot, it gives the full facts about the state of excitability of the stimulated tissues, it is a highly accurate technique if the stimulator is a good one, and it avoids all the pitfalls of rheobase and chronaxia.

ELECTROMYOGRAPHY

Electromyography has as its main aim the localization of the site of a lower motor neurone lesion.

Electrical Activity of Nerve and Muscle

When a muscle fibre contracts, its membrane becomes depolarized and this depolarization can be recorded by a needle electrode and, after suitable amplification, can be viewed on a cathode ray screen. The electrical activity associated with a single muscle fibre contracting is known as a fibrillation potential.

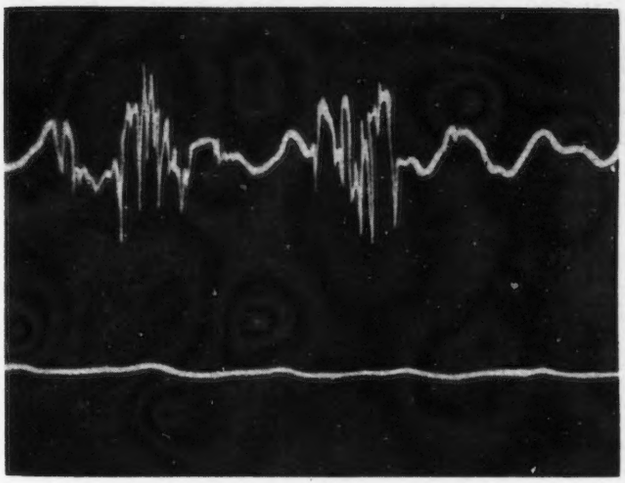

Fig. 4.—Complex or polyphasic potentials in a recovering peripheral nerve lesion.

The normal motor unit comprises an anterior horn cell, its peripheral axon and a variable number of muscle fibres—up to 180. The electrical activity of one motor unit is known as a motor unit action potential and is the algebraic summation of the muscle fibre (fibrillation) potentials of its constituent muscle fibres.

The smallest detectable voluntary contraction is associated with the discharge of one motor unit. As the contraction increases in power, more units fire off and their frequency of discharge increases. Moreover they fire off asynchronously so that muscular contraction is smooth and not jerky.

Some three weeks after a muscle is denervated, the individual fibres begin to contract spontaneously and rhythmically, and this activity can be recorded on the electromyograph as fibrillation potentials (Fig. 3). These persist until either reinnervation occurs or fibrosis ensues.

The muscle, once cut off from the trophic influence of its nerve, reverts to its intrinsic and embryologic activity of spontaneous contraction.

When reinnervation begins, the motor unit action potential is of short duration in the early stages as only a proportion of the normal complement of its muscle fibres comprise the unit. Furthermore, the myelin sheaths of the preterminal axons mature at different rates, so that within the regenerating unit there will be myelin sheaths at all stages of maturation; this leads to differences in the conduction time across the neuromuscular junctions and thus the action potential becomes temporarily dispersed. The shape of the potential has thus a characteristic complex appearance, and is known as a polyphasic potential (Fig. 4). As recovery proceeds, so these potentials become larger in amplitude, longer in duration and more polyphasic as more fibres become incorporated in the unit.

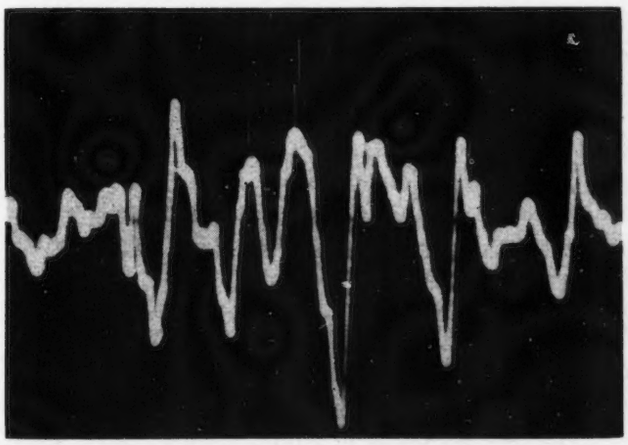

Fig. 5.—Complete interference pattern of normal motor unit activity.

Similarly polyphasic potentials will be seen in degenerating lesions of the lower motor neurone.

Electromyography will, therefore, provide evidence of denervation by detection of fibrillation potentials and evidence of regeneration by detection of polyphasic potentials. However, electromyography should not be relied on solely for deciding whether denervation is present. Fibrillation potentials may not be found in the early stages of degeneration or in partial lesions. The most reliable sign of denervation is undoubtedly the typical change in the strength duration curve—the sluggishness of response to a long duration current is also very constant.

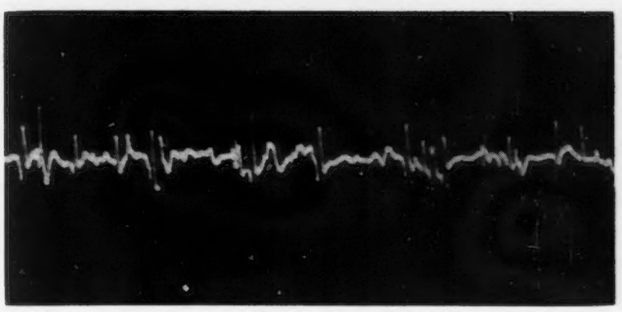

Fig. 6.—Myopathy. Note the very small short duration action potentials.

Nor may regeneration potentials be detected myographically before a kink appears on the S.D. curve, for it is to some extent a matter of chance in getting the needle into that part of the muscle that is showing regeneration—it does not always first occur at the motor point. But careful myography is highly reliable in localizing the site of lesion.

Three things must always be looked for: (1) the type of action potential initiating voluntary contraction; (2) the amount of activity present on maximal voluntary effort; (3) the type of potentials present.

Normally, voluntary contraction is initiated by small action potentials representative of the small anterior horn cells in the cord. As the contraction builds up in intensity, there is a sudden appearance of large action potentials representative of the large anterior horn cells in the cord. At the start of contraction, only a few motor units fire and,

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therefore, only a few discrete potentials are seen. As the intensity of the contraction builds up, the trace is obliterated in part by motor unit activity, the so-called partial interference pattern, and on maximal contraction in a normally innervated muscle the whole trace disappears—the so-called complete interference pattern (Fig 5).

In lesions of the anterior horn cells in the spinal cord, the small cells that are responsible for the small action potentials that initiate normal voluntary activity are destroyed first—consequently voluntary activity is initiated by *large* action potentials which may be polyphasic. This is highly characteristic of cord or myelopathic lesions. The signs of denervation—steep slope S.D. curve, sluggish response and fibrillation potentials at rest—are, of course, all present.

In lesions of the peripheral axon—so-called neuropathic lesions—polyphasic action potentials are seen because there is breakdown of the motor unit due to degeneration of nerve fibres within the units.

According to the severity of the lesion, a complete, partial or discrete pattern of activity will be seen. The severer the lesion, i.e. the more degeneration, the less the amount of motor unit activity. Again the signs of denervation on the S.D. curve and fibrillation will be present.

When the lesion is in the muscle, as in a myopathy, the action potentials will be smaller than normal, maybe polyphasic, and of lower amplitude, because muscle fibres within the motor unit are degenerating. There will be no loss of interference pattern however, because whole units are not being lost as in an anterior horn cell lesion, but only fibres within the unit (Fig. 6).

The signs of denervation are not of course present in a myopathy, as the lesion is not affecting the nerve. Thus the S.D. curve is normal, the response to long duration pulses is brisk, and no fibrillation is seen.

Progress can be checked by myography; measurement of the amplitude and duration of action potentials, and assessment of whether they are increasing or decreasing, allows an opinion to be formed as to progressive regeneration or degeneration. But changes in the S.D. curve are much more reliable and more easily recorded.

VALUE OF ELECTRODIAGNOSIS

Electrodiagnosticians are sometimes asked the question: How often do electrical methods give information not afforded clinically, and how often are they merely a comforting confirmation of what is already clinically known or suspected?

Electrodiagnosis has a real value in the following circumstances:

1. *It will indicate sooner than any other method whether a nerve has been damaged to the point of degeneration.*

Within a few days of onset of a facial palsy it is possible to tell whether the lesion is mainly neurapraxic or an axonotmesis. Wasting is a late and mild sign in the face. Patients are naturally anxious to know the prognosis as soon as possible. Response of the muscles to nerve conduction at ten days makes the good prognosis of a rapid recovery certain. Lack of response does not mean of necessity a bad prognosis, because one sees cases where the S.D. curve is almost normal, indicating no significant degeneration of the nerve, despite absent nerve conduction. It is important not to rely entirely on nerve conduction alone. If it is present, the prognosis is good and there is no need to proceed further. If absent, an S.D. curve must be plotted. Electromyography is rarely needed in such a case.

Electromyography is useful, however, when seeing a patient for the first time with a recovering facial palsy, some months after onset. The curve will obviously be a kinked curve of partial innervation. This will not tell one whether the lesion is recovering or has now reached a static stage. The detection of polyphasic potentials is a proof that the lesion is still actively recovering.

It is a mistake to carry out electrodiagnostic tests too soon. If a patient with a clinically complete radial palsy is seen only one week after onset, electrodiagnosis will not be helpful. Fibrillation does not appear for 18-21 days and the S.D. curve will almost certainly be kinked. There is no way of telling whether this is a lesion in the process of degenerating or a partial lesion. Electrodiagnostic tests should not be carried out for 2-3 weeks after onset of the lesion.

S.D. curves will indicate much earlier than clinical signs whether a lesion is only a neurapraxia or is an axonotmesis. Similarly both S.D. curves and electromyograms will show the earliest signs of regeneration some time before clinical signs appear.

The average time before appearance of kinks on the S.D. curve and the detection of a voluntary contraction is 6 weeks, and between electromyographic signs of early polyphasic potentials and clinical signs—8 weeks.

If there is a long delay—of many weeks or months—between electrical signs and clinical signs of recovery, the prognosis is poor.

In brachial plexus palsies patients often present with total paralysis in muscles supplied by some or all roots. Pain, œdema and the absence of sufficient muscle innervation to show a clinical contraction, all conspire to present a depressing outlook. Sometimes nerve conduction is seen in one or more muscles by stimulation at Erb's point; at other times there may be a slight kink in an otherwise denervated curve, or the detection of one motor unit potential only on electromyography. These are all findings of importance because they indicate that there is some continuity in the nerves and

can allow a prognosis to be given and a plan of treatment made.

2. *Electrical methods can provide evidence of an arrest in or degeneration in peripheral nerve injuries; this may not become obvious clinically for many weeks.*

Serial curves may suddenly show lack of progress. Two curves taken at a month's interval are the same. This is highly suggestive that regeneration is being prevented in a peripheral nerve lesion. In four cases a neuroma has been diagnosed by this means and confirmed at operation. Electromyography shows a replacement of polyphasic recovery potentials by normal potentials so that the signs of a partial lesion—fibrillation at rest and discrete normal potentials on activity—are seen.

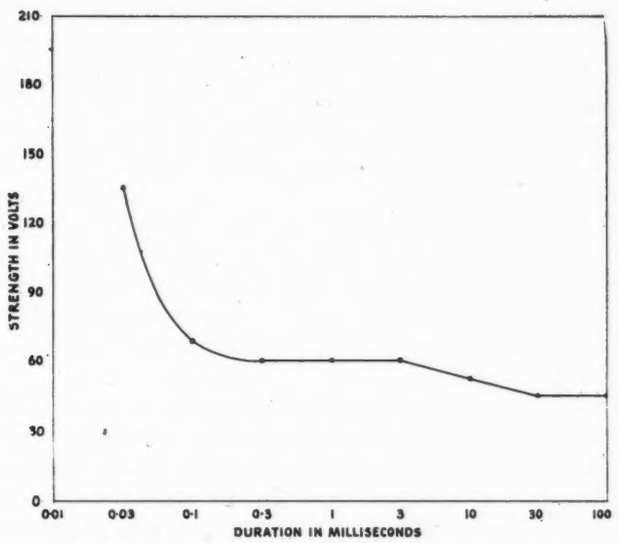

Fig. 7.—Strength duration curve on the abductor digiti minimi in a patient with the symptoms of ulnar neuritis. There is evidence of slight denervation.

3. *Electrodiagnosis will indicate the early signs of degeneration some time before clinical signs.*

Fig. 7 illustrates an S.D. curve on the abductor digiti minimi of a patient who complained of pins and needles down the inner side of the forearm following a fracture of the elbow 10 years previously. There were no objective signs of loss of sensation and no obvious muscle weakness. The curve shows clear evidence of degeneration. Electromyography may show a few fibrillation potentials, and possibly there may not be a sufficient number of polyphasic potentials for one to be sure that they are outside normal limits.

In this case the S.D. curve is definitely more helpful than electromyography.

It is well known that ulnar neuritis has a bad prognosis unless transposition is effected early. The surgeon can be confidently advised to explore the nerve on the strength of this curve.

4. *Electrodiagnosis will reveal the site of lesion in obscure clinical presentations.*

No-one claims that electrodiagnosis is necessary or indeed desirable in the obvious case of motor neurone disease or syringomyelia, but we have found electrodiagnosis most helpful in localizing the lesion in difficult cases, particularly in those where a disease presents in an unusual manner. Such for example was the case in a patient who had bilateral weakness of the calf and dorsiflexors of the ankle without any sensory loss at all, and another patient with wasting of the small muscles of both hands and loss of grip, with no other abnormal physical signs and no loss of sensation. This presentation suggested a myopathy but a combination of large action potentials initiating voluntary contraction in many parts of the muscle with much polyphasic activity elsewhere showed that both cases were in fact unusual presentations of Charcot-Marie-Tooth disease or peroneal muscular atrophy.

Indeed, the clinical picture both of a myopathy presenting for the first time in adult life and of a rapidly deteriorating myopathy in an adolescent are definitely suspect. We have recently seen a number of cases of patients developing what clinically was very like a shoulder girdle myopathy in the third and fourth decade. The electrical findings were typical of polymyositis.

The characteristic electrical signs of this condition are the signs of a mixed neuropathic and myopathic lesion. The S.D. curve may be normal or show partial denervation and there are often areas of the muscle showing a sluggish response. For this reason use of an indifferent electrode and a searching active electrode is advisable in the examination of such cases.

On electromyograms a full interference pattern of very short duration high frequency low amplitude potentials is seen with long duration polyphasic potentials in some areas.

The electrical findings thus indicate that the lesion affects the distal part of the motor neurone—the terminal part of the nerve and the outside fibres it supplies. It is, in fact, a neuromyopathy. The term polymyositis covers a multitude of etiologies. Clinically it can be used to describe any condition where diffuse symmetrical muscle wasting and weakness occurs without sensory loss. It may exist in two types—those already mentioned where the disease mimics a myopathy but occurs later in life, and those associated with other changes in skin, mucosæ, serous membranes or joints as in scleroderma, dermatomyositis or lupus erythematosus.

The detection of the typical electrical signs in this condition is important for a number of reasons. In the second group it may point to a diagnosis of collagen disease in a case with an unusual clinical picture such as a polyarthritis of doubtful etiology. In the first group it may point the way to unravelling the basic etiology.

A number of patients with idiopathic polymyositis are shown on exhaustive investigation and long-term follow-up to be suffering from a neo-

plasm, usually of the bronchus but sometimes elsewhere in the body. Some are associated with thyrotoxicosis and are probably variants of the so-called thyrotoxic myopathy.

At any rate it is important first to distinguish polymyositis from a true myopathy. Any patient with the clinical picture of polymyositis should have electrodiagnostic tests performed. The polymyositis can be treated—cortisone has had a remarkable effect in many cases.

A typical case was of a woman who was going gradually downhill with progressive loss of weight, diffuse and widespread muscle wasting, pain and a high erythrocyte sedimentation rate. There was a mild arthralgia but no true arthritis, and she had much muscle pain. She had variable skin rashes due possibly to her drug treatment; none of the rashes was typical of dermatomyositis. Repeated electrodiagnostic tests revealed typical signs of polymyositis. She lost all her pain and quickly began to regain muscle power and weight on cortisone.

These patients must be followed up and the search continued for a possible primary neoplasm, although the electrodiagnostic findings precede its discovery sometimes by years.

The differential diagnosis of small muscle wasting of the hands can certainly be helped by electromyography, as the lesion can at least be localized to the cord, peripheral nerve or muscle.

Sometimes the detection of spontaneous motor unit activity (as opposed to muscle fibre activity), whether as fasciculation or grouped discharges, can be most helpful in pointing to an irritation of a nerve root or peripheral nerve, as in degenerative joint disease or a cervical disc lesion. It is important to realize though that there is no way of distinguishing pressure on the cord due to degenerative joint disease from motor neurone disease, on electrical grounds alone. The signs are the same.

CONCLUSIONS

In conclusion, it is suggested that the following groups of patients should always be examined by electrodiagnostic techniques:

Any patient about to have a peripheral nerve injury explored—it may not be necessary.

Any patient in whom there is doubt as to the extent of a lower motor neurone lesion.

Any patient in whom it is necessary to know whether a lower motor neurone lesion is progressing, regressing or remaining static.

Any patient with the clinical signs of wasting of muscle without obvious cause.

Any patient with the signs of polymyositis.

Any patient with a suspected hysterical palsy—but S.D. curves should be plotted, not electromyograms, as the patient will naturally not oblige by showing the examiner her motor unit activity.

Any patient with a myopathy of adult life.

Any child with a lower motor neurone lesion of unknown etiology.

Provided the limitations of the methods and the specific fields of usefulness of each technique are borne in mind, great help can be afforded. The S.D. curve will assess the ratio of innervated to denervated fibres. The electromyogram will localize the lesion.

It must be remembered that these are highly accurate methods, and should be treated as such. They should always be carried out by the doctor, and always subordinate to the clinical examination.

The first weapons of the electrodiagnostician should always be the pin and the patella hammer.

I wish to thank the Director General of Medical Services, Royal Air Force, for permission to publish this paper.

THE HYPERVENTILATION SYNDROME*

J. M. KILGOUR, M.D., *Winnipeg, Man.*

IT IS SYMPTOMS that lead patients to seek medical advice, and the analysis of symptoms constitutes the most common problem faced by the practising physician. In many instances physical examination may fail to reveal abnormalities sufficient to account for the patient's complaints and, all too often, extensive laboratory studies may not help, except in a negative way. The patient naturally seeks a rational and clear explanation of his symptoms; if this is forthcoming and does not spell danger to life or health the patient is often content, even willing to accept his lot. If, on the other hand, a satisfactory account cannot be given, doubts arise, inevitably leading to fear that the true cause is unrecognized or, of even more ominous impact, that it is being hidden.

The terms "functional" and "psychosomatic" are used frequently as the explanation for symptoms which cannot be explained by findings on physical examination or even after extensive investigation. They are commonly, and of necessity, used to bridge gaps in our knowledge and understanding of the mechanisms by which symptoms arise, and of that nebulous field of structural and functional relationship between mind and body.

*Read at the Annual Meeting of the Canadian Medical Association, Edmonton, June 21, 1957.

The hyperventilation syndrome is the term applied to the effects of overbreathing. It is important for several reasons. It is a fairly common cause of distressing symptoms, whose basis the patient rarely recognizes and which may easily be missed by the physician. It is important because its symptoms may simulate symptoms of serious organic disease both to the patient and physician and, if so interpreted, lead to unwonted fears on the part of the patient and unwarranted treatment by the physician. Finally, the hyperventilation syndrome is important because it offers a physiological explanation of many obscure symptoms, and affords an excellent example of the means by which, for reasons usually though not always purely psychic, widespread physical symptoms and signs are brought about; the elucidation of the mechanism of hyperventilation offers hope that other obscure symptoms may be ultimately explicable.

By hyperventilation is meant the effect of an increase in depth and usually in rate of respiration. Its effects are caused by a sharp reduction in alveolar CO_2 concentration, which in turn causes a corresponding reduction in arterial CO_2, bringing about a rise in blood pH, a respiratory alkalosis. Concomitant with the fall in plasma CO_2 level is a reduction in oxygen dissociation from hæmoglobin, and possibly other changes such as reduction in the plasma concentration of calcium ion.

The physiological effects and the symptoms produced are widespread but, as was observed in the original description of hyperventilation by Haldane and Poulton in 1908, there is a great individual variation in symptoms produced. Just what is responsible for the resistance of some and the apparent susceptibility of others is not known, but certain factors are known which tend to enhance or diminish the symptoms produced by overbreathing. A high oxygen intake diminishes some of the effects, and conversely relative oxygen lack increases the effects, especially those on the central nervous system. A relatively low or falling blood sugar level increases the susceptibility to hyperventilation, as do the erect posture, the effect of "G", and apparently excitement or fear.

CLINICAL PICTURE

For descriptive purposes the effects of hyperventilation are most conveniently subdivided into the symptoms as they may be observed in the various systems. The brain is highly susceptible to CO_2 lack, and this is followed by a lowering of available oxygen and diminished cerebral blood flow. The changes in cerebral function are paralleled by changes in the electroencephalogram, notably a slowing of the alpha rhythm. The symptoms, largely attributable to a lowering of the state of consciousness, are variously described as faintness, giddiness, a feeling of instability, impaired power of concentration and defective memory, feeling of unreality, panic or of "losing" control. Visual disturbances such as blurring, "blackouts" or "greyouts" occur in fairly severe cases. Objective evidence is impaired memory and performance. As previously indicated, these cerebral effects tend to be minimized if oxygen intake is adequate and to be increased by low oxygen intake, as in high altitudes, and they are also increased by a relatively low blood sugar level or by the erect posture. Only rarely is consciousness actually lost, probably because the stimulus to continued overbreathing ceases as the level of consciousness falls and the resulting apnœa quickly restores the CO_2 level. One of the most important aspects of the lowered level of consciousness is the emotional release with over-reaction which commonly occurs and which is frequently accompanied by automatism with continued overbreathing of sufficient severity to perpetuate the alkalosis. As a rule, when the cerebral effects are marked they occur early and precede the more peripheral effects, tending to mask the latter.

Quite distinct from the cerebral effects are certain effects of hyperventilation on the peripheral nervous system. These symptoms are both sensory and motor, and need not be coincidental, exhibiting the dissociation of functional impairment seen in other diseases of the peripheral nerves. The sensory symptoms are paræsthesiæ, numbness and tingling, especially circumoral and in the periphery of the limbs, and these usually precede the more dramatic motor effects. Tetany with carpo-pedal spasm, formerly regarded as the hallmark of hyperventilation, is comparatively uncommon but lesser degrees of motor disturbance, notably coarse tremor, muscle cramps and pain, are common. These especially tend to occur in the muscles of respiration, the intercostals and diaphragm, and may be largely responsible for the chest pain and discomfort occurring frequently with hyperventilation which add greatly to the anxiety and fear.

The most prominent cardiovascular effects of hyperventilation are tachycardia and peripheral vasoconstriction with coldness and sweating. Ectopic beats may be observed, but I believe that they may sometimes precede the hyperventilation and in fact may be the trigger mechanism for the fear which initiates it. There is no constant change in arterial pressure, but if anything it tends to be raised. Electrocardiographic changes, notably T wave changes and prolongation of the Q-T interval, have been described in normal individuals, and there is evidence that hyperventilation may further alter the electrocardiogram in patients with pre-existing heart disease.

Air swallowing, abdominal distension and discomfort and even intestinal cramps occur and are quite possibly as much the result of the psychic effects as a direct effect of the alkalosis on the gastro-intestinal tract.

Naturally, hyperventilation is always associated with visible alterations in respiration, but only occasionally do patients appreciate this as the cause

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of their symptoms. More often than not they do not complain of any disturbance of breathing, but if they do the complaint is usually of "inability to breathe", a choking sensation, or sighing or shortness of breath. When carefully analyzed, the respiratory symptoms, as would be expected, are not associated with exertion but usually appear when the patient is at rest, often in bed or shortly after exertion has ended.

RELATION TO ANXIETY

In clinical practice hyperventilation most commonly occurs as the result of emotional stress. From time immemorial the association of emotion with disordered breathing has been recognized, whether the emotion be grief, fear, anxiety, rage or resentment. Charles Darwin, writing on the origin of the emotions in man and animal, wrote: "Men during countless generations have endeavoured to escape from their enemies by headlong flight or by violently struggling with them; and such great exertions will have caused the heart to beat rapidly, the breathing to be hurried, the chest to heave and the nostrils to be dilated—and now, whenever the emotion of fear is strongly felt, though it may not lead to any exertion, the same results tend to reappear through the force of inheritance and association." Though we may not agree with Darwin in attributing the reaction to inheritance and association, his observations are none the less true.

Cannon considered hyperventilation to be part of the homœostatic preparation for flight or battle, a preliminary reduction in CO_2 preparatory to the increased muscular exertion. When muscular effort does not ensue, the symptoms of hyperventilation result; in modern society, flight or battle is rarely the solution to alarming situations. It is now generally recognized that the hyperventilation syndrome is commonly the result of anxiety, either acute or chronic. It occurs with sufficient frequency to warrant its inclusion in the differential diagnosis of all cases with any or all of the symptoms already enumerated, whether or not they are associated with physical or laboratory evidence of organic disease, for in many instances it may be fear of real as well as imagined disease which is the underlying factor in the anxiety. Hyperventilation may also occur under unusual circumstances for reasons not entirely emotional. It is of importance in aviation medicine, particularly in high-altitude flying where anoxia is the stimulus to overbreathing and the effects of CO_2 lack may be enhanced by this anoxia, positive acceleration, "G", low blood sugar, or hunger as well as anxiety. It also may occur in prolonged respirator treatment, or under certain circumstances in anæsthesia, in central nervous system disease, and in intoxications such as salicylate poisoning. These all, however, constitute special problems beyond the scope of this discussion.

DIAGNOSIS

The hyperventilation syndrome may be an acute, occasional episode, sometimes culminating in tetany, or a more chronic state with frequently recurring episodes of somewhat lesser degree in which the symptoms tend to be cerebral, cardiovascular or peripheral but lacking the full-blown or classical pattern. It is just as important that hyperventilation be recognized for what it is not as for what it is. Attacks precipitated by acute crisis such as sudden grief or panic are usually readily recognized by reason of their explosive character, not infrequently with tetany, but almost always with a great emotional colouring which may amount to frank hysteria; here the difference from true organic emergencies is usually evident, but it is the more chronic and recurrent type that offers diagnostic pitfalls, and usually the difficulty and mistakes arise in its differentiation from organic heart disease or in recognizing it as the basis for cardiac symptoms. Heart disease receives tremendous publicity, and while most publications in the lay press purport to offer reassurance and comfort to the cardiac patient, it has been my experience that this is certainly not always the case. Fear of heart disease, cardiac anxiety in the true sense of the term, is becoming more and more common in conjunction with the hyperventilation syndrome, both in those with heart disease and those who fear it when it does not exist. There are certain important distinctions. With hyperventilation the symptoms characteristically occur while the patient is resting, albeit frequently shortly after exercise. From the literature the impression is gained that overbreathing is not an important factor in inducing angina pectoris, but I have the clinical impression that it may be a cause of some attacks of nocturnal angina which awaken patients with coronary disease, even when their tolerance to exercise is good and there is no evidence of left ventricular failure.

Hyperventilation has been confused with epilepsy but it is probably rare for true epileptics to precipitate an attack by this means. Nevertheless occasional patients may hyperventilate until consciousness is lost, or tetany may be mistaken for a convulsion.

Probably the commonest mistakes in diagnosis are in interpreting the symptoms of hyperventilation as coronary disease, effort syndrome, labyrinthitis, hypertension, postural syncope or simply "neurosis".

Fortunately it is the rule that in any given individual voluntary hyperventilation usually reproduces his symptoms. The patient is instructed to breathe deeply at a rate at least 30 per minute. Usually symptoms are induced after 30 to 60 seconds, but as long as three minutes may be required to produce them. When symptoms are induced, they serve as a confirmation of the diagnosis to the physician and as a dramatic illustration of the mechanism of production of his symptoms

to the patient. Furthermore, when symptoms have been produced, their remedy can be demonstrated either by rebreathing or by voluntary holding of the breath. This so-called "hyperventilation test" is the most valuable diagnostic procedure in establishing overbreathing as the cause of symptoms, whether or not organic disease co-exists.

TREATMENT

The treatment of the hyperventilation syndrome can be divided into three logical phases, first its recognition, secondly its demonstration by voluntary overbreathing and the demonstration of its relief by rebreathing, breath holding or exertion, and finally eradication of the basis for the emotional stress which initiates it. Frequently, and especially when fear of organic disease is the basic factor, the demonstration of the mechanism of the symptoms is all that is required, and this may also be the case when existing organic disease is the reason for anxiety. When the emotional stress is not precipitated by fear of disease but is due to other factors, psychiatric treatment may be required for the ultimate solution of the patient's problem.

SUMMARY

Overbreathing or hyperventilation is a frequent cause of distressing symptoms. It usually arises from involuntary and unconscious overbreathing because of emotional stress or anxiety. A common cause of such anxiety is fear of an organic disease, usually cardiovascular, which may or may not exist, but it also arises as the result of many severe or prolonged emotional stresses. The attacks may be acute and occasional or less severe and more frequent. The hyperventilation syndrome offers an explanation of the mechanism by which some physical symptoms arise on a purely psychogenic basis. A brief description of the symptoms is given; the most satisfactory method of diagnosis has proven to be their reproduction by voluntary hyperventilation.

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RÉSUMÉ

L'hyperventilation est une cause fréquente de symptômes pénibles. Cet excès respiratoire survient habituellement d'une façon involontaire et inconsciente au cours d'angoisse ou de tension émotive. On le retrouve communément dans la crainte d'une maladie organique habituellement cardiovasculaire qui peut exister dans les faits ou seulement dans l'imagination du malade, ou au cours de tension nerveuse grave et prolongée. On en connaît des accès aigus et espacés et d'autres moins intenses et plus fréquents. L'hyperventilation offre une explication du mécanisme par lequel certains symptômes physiques peuvent surgir de causes purement psychogéniques. La pathogénèse repose sur une diminution de l'anhydride carbonique qui entraîne une élévation du pH sanguin, une diminution de la dissociation en oxygène de l'hémoglobine et probablement une diminution de la concentration sérique en ions de calcium. Les symptômes sont décrits dans le texte. La meilleure manière de poser le diagnostic consiste à reproduire ces symptômes en exigeant du malade qu'il exagère sa respiration pendant quelques minutes.

A CRITICAL REVIEW OF ENDOSCOPY*

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I HAVE RECENTLY reviewed the endoscopic records of the Royal Victoria Hospital both from the point of view of changes that have developed in the incidence of lesions encountered and from the point of view of technique. The review covers a period of 20 years during which time I have been associated with this specialty. It was undertaken with the hope that it might explain why many chest physicians and surgeons are becoming so interested in endoscopy. Is it because the otolaryngologists have not been maintaining a good service or have there been changes in chest pathology that have brought the intrabronchial area closer to the field of the chest surgeon? Another object of this review was to point out the endoscopist's contribution to the alleviation of disease in the respiratory and upper gastro-intestinal tracts. In our hospital we have been sympathetic towards the thoracic surgeon who desires to do his own endoscopy. After all, he carries the responsibility when it comes to removing lungs and lobes. It is he also who must open the chest when complications occur as the result of endoscopy.

The subject of bronchoscopy has been approached from three aspects: (1) carcinoma of the lung; (2) 100 routine examinations; (3) a review of the examinations made in 1956.

Carcinoma of the Lung

The review began with a study of the records of 100 patients who had been bronchoscoped and in whom carcinoma of the lung was confirmed histo-

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Presented at the Annual Meeting of the Canadian Otolaryngological Society, Banff, Alta., June 1957.

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logically. It was not necessary to go back more than three years to select 100 suitable cases. The cases belonged to many members of the hospital staff and the bronchoscopy was carried out by the various members of the ear, nose and throat service and by one qualified thoracic surgeon. There is something sinister about being able to pick out 100 well-documented cases of carcinoma of the lung in such a short period of time when the records show that only seven cases were recorded in the year 1937. The majority of these patients had extensive lesions with relatively long histories of cough, chest pains and bloody sputum. Four reported because of routine radiological evidence of disease without symptoms or signs. It was obvious from the records and our present knowledge that many of these cases should have been bronchoscoped much earlier than they were.

It was interesting that in 70% of these cases the lesion could be sufficiently well seen by the bronchoscopist to permit the taking of a biopsy. In 51% of the total number of cases the bronchoscopist's biopsy permitted a histological diagnosis. Material for cytological examination was procured in 49 cases, but in only one instance was the cytological examination positive when the result of biopsy was negative. The great majority of the 30 lesions not biopsied were either not seen by the bronchoscopist or were in the upper lobe bronchi and relatively inaccessible. In these cases and in those in which the bronchoscopic biopsy failed to give the diagnosis, the latter was made on material procured from aspirated pleural fluid, from cervical mediastinal biopsies, from lung biopsies and from autopsy. Twenty-three of the patients in this series had had bronchograms; the majority of these were patients in whom the lesions were unseen or inaccessible to the bronchoscopist.

One Hundred Routine Examinations

One hundred consecutive bronchoscopic examinations from records were picked out on an alphabetical basis over the past three years, for review. The object here was to get some idea of the variety of the material presenting for bronchoscopic examination, and to compare the bronchoscopist's diagnosis with the final diagnosis of each patient on discharge from hospital.

A most interesting revelation was that in this group there were 23 carcinomas of the lung, and one benign tumour which required lobectomy.

Of the 23 carcinomas, 17 lesions were seen, biopsied and diagnosed as such on the clinical appearance; however, in only 13 did the biopsy taken by the bronchoscopist prove the lesion histologically. Two other cases were diagnosed as carcinoma because of concentric compression stenosis of the bronchus. One of these was proven by mediastinal biopsy and the other by autopsy. Of the remaining eight cases, two were peripheral lesions and could not possibly have been seen through the bronchoscope, one was a carcinoma solidum diagnosed by lung biopsy, and five lesions were in the upper lobe bronchi.

In 21 cases of carcinoma cytological specimens were collected at the time of bronchoscopy, but in only two cases was the report positive; in two others it was merely suggestive. This seems to be a very low yield for cytology. Although the collection of proper material may be a major difficulty, it cannot be the whole answer. The pathologist must also share in the responsibility.

Of the 100 cases, 85 showed agreement between the bronchoscopic findings and the final diagnosis. The 15 cases in which the final diagnosis did not agree with the bronchoscopic findings included 4 cases of carcinoma of the lung undiagnosed by the bronchoscopist; 3 cases of tuberculosis (1 negative findings, 2 cases of tuberculous granulation thought to be carcinoma but proved on section to be tuberculosis); 4 cases of bronchiectasis (3 with negative findings reported).

The high incidence of neoplasms in this series is impressive, and is no doubt influenced by the fact that the Royal Victoria Hospital has a large chest clinic attracting surgical chest cases which include carcinoma. The decline of chronic inflammatory lesions in the chest as a result of improved medical and surgical treatment is another reason for the relatively high incidence of carcinoma.

It is significant that there were no foreign bodies in the series.

Bronchoscopy During the Year 1956

To obtain a reasonable check on the high incidence of carcinoma and a more complete picture of the material passing through the endoscopic clinic, it was decided to review all the records of patients having had laryngoscopic, bronchoscopic and œsophagoscopic examinations in 1956.* During that year 172 patients had a total of 182 bronchoscopic examinations. The final diagnoses included the following conditions, all of which have a bearing on carcinoma of the lung:

Carcinoma of the lung	34
Bronchiectasis	19
Unresolved pneumonia	25
Hæmoptysis	21
Chronic bronchitis	15
Cough, undiagnosed	6

The group that interests us most is the large number of carcinomas of the lung: 34 of 172 or about 20% of the patients on whom bronchoscopic examinations have been made. Twenty-nine of the carcinomas were thought to have developed within the bronchus. However, one of these was an adenocarcinoma and may have had another origin. Five were considered to be metastatic (three from

*Twenty-five gastroscopic examinations have been omitted from the review. These examinations in the Royal Victoria Hospital have for the past few years been made entirely by the gastroenterologists. The number of examinations is small and no attempt will be made here to judge their value.

carcinoma of the breast, one from carcinoma of the stomach and one from carcinoma of the prostate). Thirteen of the 29 bronchial carcinomas were diagnosed by intrabronchial biopsies and one by intrabronchial cytology. Cytology specimens were sent to the pathology department from 60 bronchoscopic examinations and eight were reported positive for malignancy. In only one was the positive cytology associated with a negative biopsy.

Eleven cases showed concentric compression stenosis of the bronchus. In two of these a positive diagnosis was procured through the bronchoscope, one by biopsy and one by cytology. In one case, biopsy was twice negative and the diagnosis was made at autopsy. Four were proven by mediastinal biopsies. In four the biopsy finding was recorded as squamous metaplasia but in each instance the case was considered carcinoma.

Three patients with negative intrabronchial biopsies were considered to have carcinoma on clinical, bronchoscopic and radiological evidence. In one of these the biopsy showed squamous metaplasia and atypical cells. In three cases with negative intrabronchial biopsies the diagnosis was made by mediastinal biopsy, at autopsy and on lung removal respectively.

In summary, 14 of the 29 bronchogenic carcinomas were proven by intrabronchial biopsy or cytology, two at autopsy, four by mediastinal biopsy, one by removal of the lung in which intrabronchial biopsy revealed squamous metaplasia. In 5 cases, biopsy suggested squamous metaplasia but the case was considered to be carcinoma. Three cases with negative biopsies were considered to be carcinoma on clinical, bronchoscopic and x-ray evidence.

There were five metastatic carcinomas. In one the bronchoscopic findings were normal—the patient had carcinoma of the stomach with clinical and radiological signs of metastases in the lung. This is the only case in this entire series of carcinomas in which a definite lesion or some gross abnormality was not seen by the bronchoscopist. In none of the metastatic cases were intrabronchial biopsies obtained, but in two positive mediastinal biopsies were procured.

An interesting group of bronchogenic carcinomas are the 11 cases with concentric compression stenosis of the bronchus. These lesions were about equally distributed between upper and lower lobes, the majority in the right side of the chest. The concentric compression develops from the pressure of lymph glands about the bronchus. The lesion may not necessarily be carcinoma. In this series similar stenoses were seen in two cases of Hodgkin's disease and in one of tuberculosis and were proven by mediastinal biopsies.

In only one of the group of 11 cases of concentric compression stenosis was a positive biopsy procured from within the bronchus; one other cytological examination was positive, i.e., the finding was positive in 20% of these cases whereas in the remaining cases positive intrabronchial biopsies were procured in 12 out of 17 or 75%. One should approach such a lesion with a great deal of caution, because if the operator takes too deep a specimen, he runs the risk of starting a serious hæmorrhage. It is not to be forgotten that fatal hæmorrhages do occur as the result of bronchoscopy (one occurred in this series).

The 25 cases of pneumonia represented a group of pneumonic lesions which had not responded to the usual antibiotic therapy in the expected manner. In many instances bronchoscopy was done to rule out the possibility of bronchial carcinoma. For the same reason, bronchoscopy was done in the 21 cases of hæmoptysis and in the majority of cases of chronic bronchitis, undiagnosed cough and bronchiectasis. It would therefore appear that over 75% of our bronchoscopic examinations have been made with a view to either finding or ruling out the presence of carcinoma of the lung.

With the exception of a small number of foreign body extractions and a few cases of aspiration of secretions in atelectasis, bronchoscopy has become a diagnostic procedure. This is in marked contrast to the trend that prevailed 20 years ago when the majority of bronchoscopic examinations were performed for therapeutic reasons.

In 1937 chemotherapy was just beginning to enter the scene. Most of the 307 bronchoscopic examinations and Lipiodol injections were done that year because of chronic suppurative disease of the lung. Several examinations were often made on the same patient. One patient with bronchiectasis underwent bronchoscopy 43 times in that year, another 33 times. Twenty-six patients had a total of 223 examinations. These multiple examinations were practically limited to bronchoscopy and laryngoscopy and many were done for therapeutic reasons.

In 1947 the picture changed considerably. The number of bronchoscopic examinations was then reduced to 159, whereas the number of patients treated increased to 131. Only one patient had as many as five examinations; another had four. Twenty-five patients had a total of 55 examinations. In ten years the average number of examinations per patient was reduced from 3 to 1.2. Chemotherapy and improved chest surgery had cleared up much of the chronic bronchitis and bronchiectasis. By 1947 the number of intrabronchial biopsies had increased fourfold in a decade. The records of the past 10 years make it obvious that bronchoscopy has become almost completely devoted to the search for carcinoma of the lung.

ŒSOPHAGOSCOPY

The problems encountered in diseases of the œsophagus have not changed much in 20 years. The improved use of various forms of dilators has reduced the need for repeated examinations in some cases.

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Between 1937 and 1947 the number of œsophagoscopies increased from 40 to 97. I believe that this increase was influenced by chemotherapy, which made it a safer procedure, and by recent progress in thoracic surgery which may have stimulated more interest in œsophagoscopy.

Sixty-two œsophageal examinations were carried out on 58 patients in 1956. About three-quarters of these were done by members of the Department of Ear, Nose and Throat, using mostly general anæsthesia, whereas the remaining cases were done under local anæsthesia by gastroenterologists. Of the 58 patients examined in 1956, 12 showed no evidence of disease in the œsophagus either by x-ray or by œsophagoscopy. Two complained of bleeding and 10 of dysphagia.

Of the remaining 46 patients the diagnosis were as follows:

Carcinoma in upper third	4
Carcinoma in lower third	4
Stenosis of the upper third (traumatic)	1
Stenosis of the lower third	3
Cardiospasm	3
Stricture resulting from ingestion of lye	1
Diverticulum (upper third 4, middle third 1)	5
Œsophagitis	3
Acute epiglottitis	1
Œsophageal varices	1
Foreign bodies	7
Thickening of retrotracheal space in septicæmia	1
Hiatal hernia	12

The number of these examinations is too small to allow of much comment on the incidence of any particular group of cases. It is interesting, however, that there were as many as 12 hiatal hernias. Four of these patients were women and eight were men.

All the cases of hiatal hernia were diagnosed by preoperative radiographs except for one case which was doubtful until biopsies were taken from above and below the junction of œsophageal and gastric mucosa and the positions of the biopsies marked with metallic clips. The areas were then shown by x-ray to be well above the diaphragm. All the cases were of the sliding type except one diagnosed as a congenital short œsophagus in a 60-year-old patient. This diagnosis of a congenital as opposed to an acquired short œsophagus is open to question because of the late onset of symptoms.

HAZARDS OF ŒSOPHAGOSCOPY

During the period reviewed two serious complications resulted from œsophagoscopy: (1) ruptured lower third of the œsophagus: (2) upper mediastinal abscess. By extending the period to cover 15 consecutive months, it is possible to present two additional complications of œsophagoscopy. These cases are presented with the hope that they will demonstrate the need for serious study of any patient requiring such an examination; the need for preoperative radiographs of the chest; lateral radiographs of the neck for lipping of the bodies of cervical spines; opaque radiographs of the œsophagus, and the need for good relaxation of the patient during the examination.

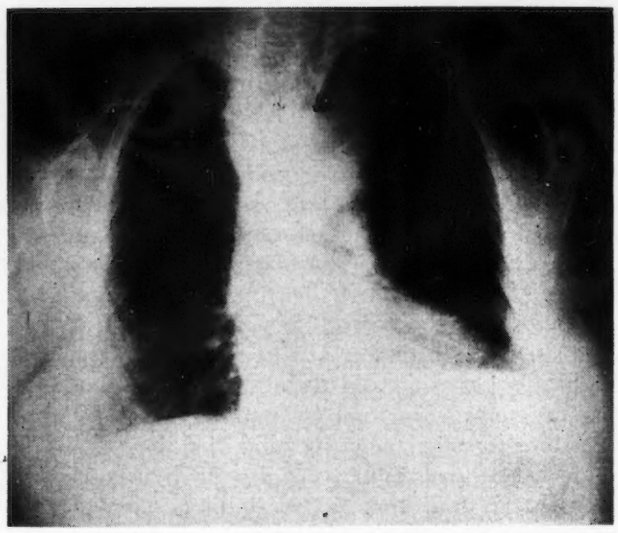

Fig. 1. (Case 1).—Mediastinal abscess five days after operation.

CASE 1.—A woman with radiological evidence of a hiatal hernia developed an upper mediastinal abscess (Fig. 1) five days after an uneventful œsophagoscopy under general anæsthesia. A subsequent tracheotomy and drainage of the abscess were necessary. The patient recovered.

CASE 2.—A man suffering from cardiospasm complained of abdominal pain a few hours after œsophagoscopy. The abdomen was rigid. Air was visible under the diaphragm by x-ray. The œsophagus was exposed the same day and was found torn in the lower third. This tear was repaired and a myoplasty was performed to correct the cardiospasm. Recovery was then uneventful.

CASE 3.—An infant, aged 11 months, was admitted from another hospital after œsophagoscopy and removal of part of a metallic foreign body. On admission to our hospital the remaining portion of the foreign body was outside the œsophagus. This was removed by the thoracic surgeon and the œsophagus was repaired. Recovery was then uneventful (Figs. 2, 3 and 4).

CASE 4.—A man suffering from dysphagia developed emphysema of the neck immediately after œsophagoscopy. The cervical mediastinum was opened but no lesion was found. The patient's condition deteriorated over a period of 10 days and he died. A partial autopsy revealed an anterior mediastinitis with most evidence of irritation within the trachea and no evidence of any lesion in that part of the œsophagus seen at autopsy (Fig. 5).

Œsophagoscopy in Case 3 in which there was a large thin metallic body in an infant under one year of age could be looked upon as a very hazardous procedure. However, there was no special reason to expect any complication to follow

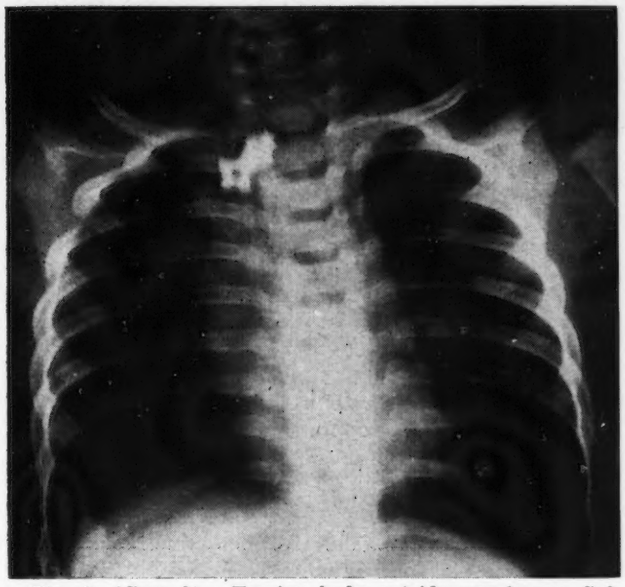

Fig. 2. (Case 3).—Foreign body outside œsophagus. Subcutaneous emphysema of the neck. Picture taken before admission.

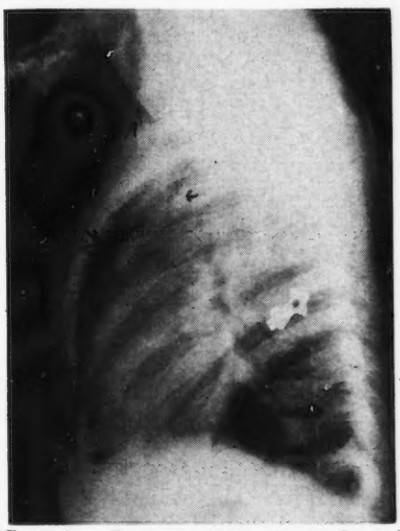

Fig. 3. (Case 3).—Picture taken about three hours later than Fig. 2. Note the air in the mediastinum and change in position of the foreign body.

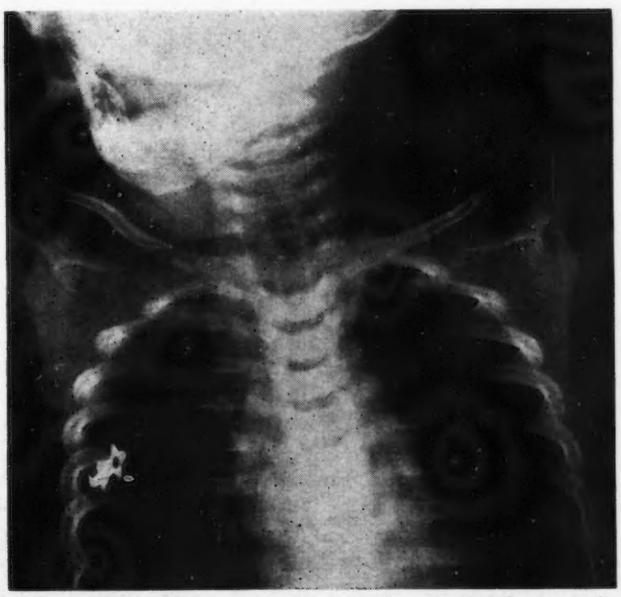

Fig. 4. (Case 3).—A.P. view of the chest taken at the time of Fig. 3.

œsophagoscopy in Cases 1, 3 and 4. This only emphasizes the importance of careful preoperative examination to make sure that the obvious hazards are detected. Among these are aneurysms of the aorta; diverticula at various levels of the œsophagus; congenital anomalies of the aorta including a right-sided aorta passing behind the œsophagus; lipping of the bodies of the cervical vertebræ.

LARYNGOSCOPY

The volume of clinical material examined by direct laryngoscopy has not varied much over the past 20 years with one exception. A few cases of tuberculosis required intralaryngeal treatment before the advent of streptomycin. These cases are now rarely seen.

In the past 10 years the suspension laryngoscope has been increasingly used in our clinic. The number of cases examined by this instrument is still small but is increasing and should continue to increase because of the tremendous improvements in general anæsthesia.

Eighty-seven laryngeal examinations were made on 63 patients during the year 1956; of these 21 were females and 42 males. Only five of these patients were children and in this group were two cases of foreign bodies. The lesions found included the following:

Benign tumours	28
Carcinoma	8
Chronic laryngitis	7
Non-specific laryngitis	3
Paralysis vocal cord	1
Inter-arytenoid ulcer	1
Traumatic laryngitis	1
Internal laryngocele	1
Laryngeal malacia	1
Foreign bodies	2

It is obvious from the above diagnoses that at least 80% of these examinations were made for the purpose of diagnosing or excluding malignancy in one group and removing benign tumours such as polyps and singers' nodules in another. One unusual case appeared during the year, an internal laryngocele which had developed to the stage of causing marked dyspnœa (see Fig. 6). Tomograms of the larynx suggested the diagnosis, and no surface ulceration could be seen through the anterior commissural laryngoscope or when the larynx was suspended. Malignancy was not entirely excluded until the larynx was opened and the sac removed.

It is interesting to go back 20 years and to see how that period compares with the present one. In 1937, 99 direct laryngoscopic examinations were made on 72 patients. Thirty-eight biopsy specimens were taken from these patients, which suggests that the operators at that time were as much aware of the great need for histopathological diagnosis of lesions in this area as they are today. In 1947, 115 examinations were made on patients and 40 biopsies were taken for pathological study.

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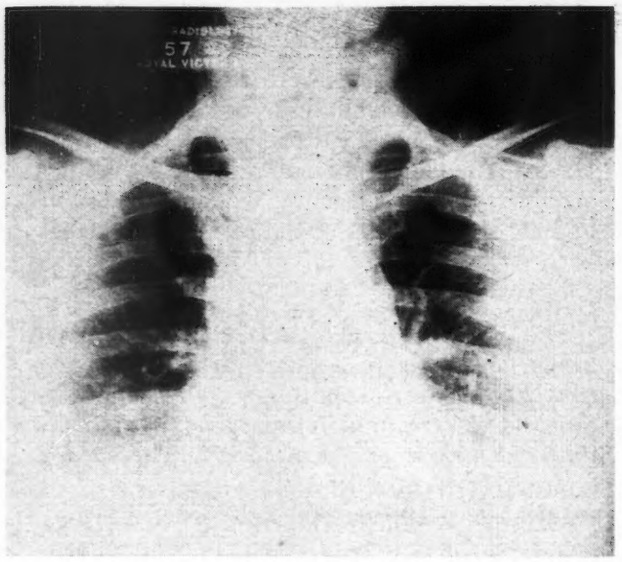

Fig. 5. (Case 4).—Chest radiographs 24 hours following œsophagoscopy. Air was demonstrated in the subcutaneous tissues of the neck and in the mediastinum.

It should be pointed out that during these past 20 years direct laryngoscopy has become an integral part of the anæsthetist's technique. I do not need to comment on how many thousands of general anæsthetics with intratracheal intubations are done in any of our larger hospitals in the course of a year. These all demand as many exposures of the larynx. Some of our anæsthetists have become very adept at exposing the larynx and passing intratracheal tubes and some are able to recognize lesions about the larynx.

Direct laryngoscopy and intubation may now be the first measure taken to establish an airway in a patient who will eventually require a tracheotomy. It has replaced the need for the so-called emergency tracheotomy. In modern hospitals today most tracheotomies should be orderly procedures preceded by intubation.

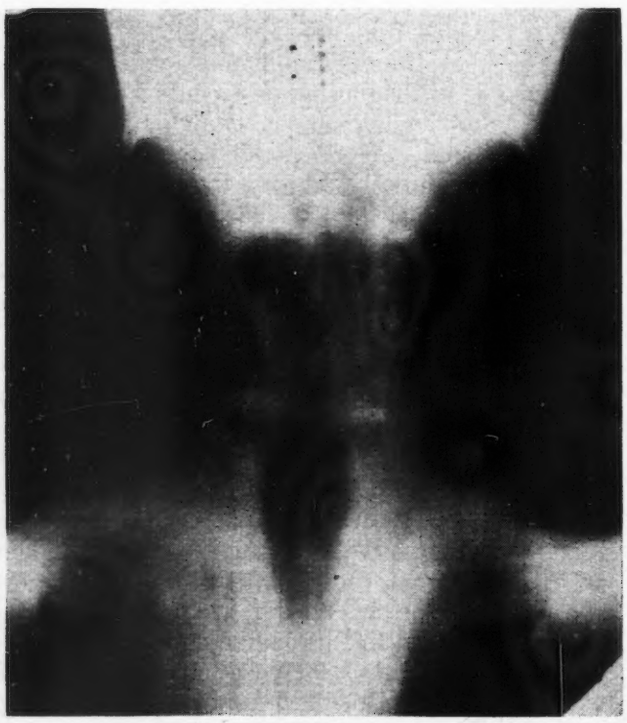

Fig. 6.—Internal laryngocele, right side.

SUMMARY

The records of patients admitted to the Royal Victoria Hospital, Montreal, for endoscopic examination of the larynx, bronchi and œsophagus during the past 20 years have been reviewed and reported.

The rapid change in the incidence of types of lung lesions following the advent of chemotherapy and coincident with the increasing incidence of carcinoma of the bronchus is emphasized. As a result, over 75% of bronchoscopic examinations are now being made for the purpose of finding or excluding carcinoma.

Twenty per cent of patients bronchoscoped in 1956 had carcinoma of the lung. The total number of such carcinomas was 34, of which 29 were squamous cell in type and were considered to have originated in the bronchus. Check surveys over the past three years show this estimate to be conservative.

Seventy per cent of the lesions in cases of lung cancer are identified by the bronchoscopist and in over half of the cases positive biopsies are procured through the bronchoscope. Instances in which the thoracic surgeon has established the diagnosis by mediastinal biopsy are noted. The frequent occurrence of concentric compression stenosis of a bronchus is reported. The majority of these stenoses are due to underlying carcinoma but may also be due to Hodgkin's disease or to tuberculosis. The most successful approach to biopsy in these cases has been by way of the cervical mediastinum.

The review shows no evidence of radical changes in the incidence of lesions encountered in the œsophagus. Increasing numbers of examinations on the œsophagus appear to be based on the stimulating effect of improved techniques in thoracic surgery and better radiography. The relatively large number of hiatal hernias is explained on this basis.

Complications of œsophagoscopy are reported. Various hazards in this examination are discussed and some are demonstrated by radiographs.

The writer concludes that 80% of direct laryngoscopic examinations fall into two categories. In the first group the primary purpose of the examination is to diagnose or exclude carcinoma, and in the second group the purpose of the examination is to remove benign tumours such as polyps and nodes from the vocal cords.

APPENDIX

ANÆSTHESIA

Agreement on the proper preparation for endoscopic examination is far from universal. Particularly is this true of whether the examination should be carried out under general or local anæsthesia. Some other general principles are universally recognized. Every operator is anxious to have a safe anæsthetic and at the same time a well-relaxed patient. There are certain conditions such as postoperative atelectasis, and certain inflammatory chest conditions in which coughing must not be inhibited any longer than necessary and for such reasons local anæsthesia might be preferred. On the

other hand, when a foreign body is to be removed from the œsophagus, relaxation of the patient is most important and for that reason a general anæsthetic might be preferred. I believe that the choice of anæsthesia frequently depends to a large extent on the availability of good general anæsthesia. There have been tremendous strides in perfecting general anæsthetics in the last ten years. The introduction of curare and intravenous thiopentone (Pentothal) made it possible to reduce the amount of anæsthetic and at the same time increase the relaxation of the patient. This was desired in bronchoscopy, œsophagoscopy and laryngoscopy.

In 1937, bromethol (Avertin) was used in a few cases. Its use necessitated meticulous preparation of the patient by repeated enemas. This made it difficult to arrange an operating schedule. The anæsthetic was good but the patient did not wake up for hours after the examination, which was not what was desired in endoscopy. After a few months Avertin was abandoned, and it is interesting to note that in 1947 only five general anæsthetics were given for 159 bronchoscopic examinations. In 1956, 82 general anæsthetics were given for 182 bronchoscopies. The majority of examinations by members of the ear, nose and throat staff were made under general anæsthesia. The same trend in anæsthesia is noted in laryngoscopy and œsophagoscopy, as indicated by the following figures:

ANÆSTHESIA IN BRONCHOSCOPY

Year	*No. of examinations*	*Local*	*General*
1937	269*	223	46
1947	159	154	5
1956	182	100	82

*38 Lipiodol injections omitted.

ANÆSTHESIA IN ŒSOPHAGOSCOPY

Year	*No. of examinations*	*Local*	*General*
1937	42	27	15
1947	95	71	24
1956	62	20	42

ANÆSTHESIA IN LARYNGOSCOPY

Year	*No. of examinations*	*Local*	*General*
1937	99	81	18
1947	115	94	21
1956	87	23	64

At the present time our general anæsthetic for these examinations consists of intravenous Pentothal, nitrous oxide and oxygen, and the topical application of 4% lidocaine (Xylocaine) to the hypopharynx, larynx and trachea. The total amount of the latter does not usually exceed 4 c.c. For additional muscular relaxation a 0.1% succinylcholine intravenous drip is used.

In the preparation of the patient for local anæsthesia 5 to 10% cocaine has been in use in this clinic for years. Recently Xylocaine 4% has been more popular. Xylocaine differs from cocaine in having no vasoconstrictor effect and being very rapidly absorbed. It gives a fast and profound anæsthesia whose duration is shorter than that provided by cocaine. Pontocaine resembles Xylocaine in that it has no vasoconstrictor effect. It has been used on only a few patients. Because they do not produce vasoconstriction, these drugs are rapidly absorbed and may be even more toxic than cocaine.

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RÉSUMÉ

L'auteur fouilla les dossiers des malades admis à l'hôpital Royal Victoria de Montréal pour examen endoscopique du larynx, des bronches et de l'œsophage pendant les vingt dernières années. Il a été frappé par le changement dans la fréquence des genres de lésions pulmonaires qui suivit l'emploi de la chimiothérapie et coïncida avec un accroissement dans le nombre de cancers des bronches. Au delà de 75% des examens bronchoscopiques sont maintenant pratiqués dans le but de dépister le néoplasme. En 1956, 20% des patients ayant subi une bronchoscopie étaient atteints de cancer du poumon. Le total s'élevait à 34 cas dont 29 étaient de type pavimenteux et considéré comme issu des bronches. Ce chiffre est plutôt faible en comparaison de ceux obtenus dans d'autres enquête au cours des trois dernières années. Le bronchoscopiste peut identifier 75% des lésions de cancer, et dans 50% des cas il peut obtenir une biopsie positive au moyen de son instrument. Dans certaines circonstances le chirurgien thoracique peut établir un diagnostic à l'aide d'une biopsie médiastinale. La sténose d'une bronche par compression concentrique est une lésion qui s'observe fréquemment. Dans la majorité de ces cas on peut soupçonner le carcinome quoique la maladie de Hodgkin ou la tuberculose peuvent être incriminées. Les meilleures biopsies sont alors celles que l'on obtient par l'entremise du médiastin cervical. Au cours de ces vingt années les lésions de l'œsophage n'ont guère changé. L'augmentation dans la pratique de l'œsophagoscopie est sans doute le résultat du progrès accompli dans la chirurgie thoracique et dans la radiologie. C'est aussi pourquoi les hernies diaphragmatiques semblent plus nombreuses. Les dangers de l'œsophagoscopie sont soulignés.

CYCLOSERINE-ISONIAZID COMBINATION THERAPY IN PULMONARY TUBERCULOSIS

Eighty-one new, previously untreated cases of pulmonary tuberculosis were treated by Epstein *et al.* (*Dis. Chest*, 33: 371, 1958) with an oral cycloserine-isoniazid combination for six weeks to 16 months. Clinical improvements, reduction of fever, lessening of the volume of sputum, and gain in weight occurred promptly in every case. In addition, the administration of a single capsule containing cycloserine and isoniazid, twice daily, was more acceptable to the patients than the usual isoniazid-PAS combination. Within six weeks, 40% of the chest films showed evidence of improvement. The figure rose to 74% in 12 weeks, and to 93% of 48 subjects treated for six months. Evidence of reduction in the bacillary content of the sputum was obtained within six weeks of treatment. Within three months, 80% of 64 sputa were negative on culture, and at six months the figure rose to 87%. Sensitivity of tubercle bacilli to cycloserine fell slowly and slightly during prolonged treatment with the larger doses. From 0.5 g. of cycloserine per day, there was no evidence of decreased sensitivity. Resistance to isoniazid developed during the administration of the cycloserine-isoniazid combination at approximately the same rate as is seen when isoniazid is given alone. There was only one untoward reaction, which did not necessitate discontinuance of treatment.

It is concluded that a combination of 0.25 g. cycloserine and 0.15 g. of isoniazid given twice daily is effective and safe therapy against previously untreated cases of pulmonary tuberculosis. Clinical results were considered to be superior to the usual isoniazid-PAS therapy, both in speed and degree of response, as gauged by radiological changes and sputum conversion.

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Case Reports

ATTEMPTED HOMO-TRANSPLANTATION OF BONE MARROW IN A PATIENT WITH LEUKÆMIA*

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THE REPORT by Barnes *et al.*[1] that the generalized lymphoid leukæmia of the C.B.A. mouse could be successfully treated in a proportion of cases by giving whole body irradiation in doses approximating to the 100% lethal dose followed by intravenous injections of isologous and homologous bone marrow, has raised hopes that a similar form of treatment might be applied successfully in leukæmia in man. It was thought initially that the action of bone marrow in modifying the effect of radiation was due to humoral factors,[2] but more recently the evidence would seem to suggest that the marrow of the irradiated animal is actually destroyed and the injected hæmopoietic material repopulates the recipient's marrow sites. The acceptance of foreign tissue by the recipient is rendered possible by a reduction of the immunological defences of the host induced by x-radiation.

Congdon, Uphoff and Lorenz[3] demonstrated that rat bone marrow could be used successfully in mice to prevent radiation death. Ford *et al.*,[4] using a chromosome marker technique, were able to show that when donor animals with an atypical marked chromosome were used and the irradiated mice injected with this marrow, the irradiated mice not only survived but presented marrow which appeared to be normal and contained the atypical marked chromosome. Nowell *et al.*[5] demonstrated that rat bone marrow injected intravenously into heavily irradiated healthy mice was successful in preventing radiation death; the mature granulocytes of rats are strongly positive for alkaline phosphatase and the same cells of mice completely negative. Two to four weeks after the transplantation, the entire population of the bone marrow granulocytes was made up of alkaline phosphatase positive cells. Further work by Merwin and Congdon[6] seems to demonstrate fairly clearly that the marrow spaces of irradiated mice are repopulated by donor cells.

When mice were irradiated and received rat bone marrow, on about the 20th day after treatment and continuing through the 5th and 6th weeks, a secondary body weight loss was observed in several animals. During this critical period an increased number of deaths was observed. It was suggested that a delayed immunologic response of the irradiated host to the foreign transplanted tissue was occurring, resulting in a chronic *in vivo* antigen antibody response, and that this was responsible for the poor physical and metabolic condition of these animals.[7]

Evidence of repopulation of intravenous bone marrow after whole body irradiation has been reported in canines[8] and in primates.[9] A brief review of the present position regarding the experimental treatment of whole body irradiation injury was published recently by Congdon.[10]

The optimum dosage of deep x-ray for a successful homotransplantation in man is not known. From first principles, however, it would seem that the object of whole body irradiation is to eradicate and destroy leukæmic tissue in the bone marrow and to impair temporarily the immunological responses of the recipient to such a degree that the recipient's cells are unable to recognize the injected donated material as foreign tissue and, therefore, allow repopulation of the marrow sites. The question of dosage is critical; theoretically, it would seem that if too small radiation dosages are given, neither the leukæmic tissue nor the immunological responses will be sufficiently affected to allow the marrow transplant to "take". On the other hand, if too high a dose of whole body radiation is given, damage to tissues other than the hæmopoietic system (for example, the gastro-intestinal tract) may be fatal.

The application of a dose of x-radiation in the lethal range in man raises the question whether it is right ethically to attempt this form of therapy. In the present instance, the standard forms of therapy had been applied and it was felt by us that there seemed to be no hope that any other form of therapy would be successful. It may be that the attempt to treat this patient with whole body irradiation was made too late, but we feel that in the light of present knowledge, it would be very wrong to attempt this form of therapy until there was ample evidence that the patient had become refractory to all forms of treatment or unless evidence of successful application of whole body irradiation and bone marrow injection is reported in man. With these reservations, we agree with the observation of Thomas *et al.*:[11] "If infusion of marrow can induce recovery in a mouse or monkey after lethal irradiation, one had best be prepared with this form of treatment in man."

The paucity of information regarding the effects of whole body radiation and marrow infusion in man has prompted us to make this report.

CLINICAL HISTORY

R.B., a white male farmer, was first seen at the Allan Blair Memorial Clinic on June 23, 1955.* At this time he was 51 years of age. He complained of tiring easily and of an aching discomfort in the left upper quadrant of the abdomen. On physical examination, he looked slightly pale. Several small discrete lymph

*From the Allan Blair Memorial Clinic, Regina.

*Referred by Dr. D. R. Rudd of Moose Jaw.

nodes were palpable in the neck, axillæ and groins. Examination of the abdomen revealed that the spleen was palpably enlarged 7 cm. below the left costal margin. General physical examination revealed no other abnormality.

The Hb value was 11.8 g. % (76%) and the total white cell count 171,500 per c.mm. A differential count revealed that 98% of the cells in the peripheral blood were lymphocytes. The sternal marrow was hypercellular and was overrun by small mature lymphocytes. A diagnosis of chronic lymphatic leukæmia was made.

As the patient was suffering little discomfort, it was decided to follow his clinical course but not to apply any specific form of therapy. Treatment with cortisone was started on December 1, 1955. After initial dosage of 100 mg. three times a day for four days the dose was reduced to a maintenance level of 100 mg. daily for a month and then to 75 mg. daily. Maintenance therapy with 20 mg. of prednisone daily was substituted and under this regimen the patient felt well although his white cell count remained elevated. On May 29, 1957, his Hb value was 11.5 g. % (74%) and the white cell count 99,500 per c.mm. By July 26, 1957, his Hb value was 5.9 g. % (38%) and the white cell count 87,500 per c.mm. He was treated with blood transfusions and his Hb level gradually rose to 10.9 g. % (70%) and he felt much better. Treatment with C.B. 1348 (Chlorambucil) 2 mg. 3 times a day was started. No improvement occurred however, and on August 19, he was found to have multiple petechial hæmorrhages scattered over his body surface. The spleen had enlarged greatly and was now 23 cm. below the left costal margin. Treatment with C.B. 1348 was stopped.

As the platelet count was 35,160 per c.mm., it was thought that radiotherapy might be dangerous. In view of the findings of Ranney and Gellhorn[12] with massive dosage of prednisone in the acute leukæmias, it was decided to apply this form of therapy. Prednisone 100 mg. 4 times a day was started on August 31 and continued until September 4 when the dosage was reduced to 50 mg. q.i.d. During the period of heavy dosage with steroids, the patient developed some œdema of the ankles but there was no disturbance of his serum electrolytes. A "diabetic" glucose tolerance curve was observed but this returned to normal after cessation of therapy. No improvement in his condition was noted with this treatment.

By October 28, 1957, in spite of repeated blood transfusions, the patient's Hb value was 6.1 g. % (39%) and the total white cell count 8800. The differential distribution showed 89% lymphocytes. No reticulocytes were found in the peripheral blood.

At this stage it was thought that the patient had entered an aplastic phase. Whether this was due to the therapy with C.B. 1348 or to the natural course of the disease was not clear. It was felt that there was no further therapy to be offered to the patient. His platelet count was sufficiently low to preclude x-ray therapy. He had already failed to respond to large doses of prednisone. Treatment with C.B. 1348 had not been successful and repeated blood transfusions had failed to elevate his Hb above its low level. It was agreed that treatment with whole body radiation and subsequent bone marrow transfusions should be attempted.

The patient was given 50 mg. of cortisone by intramuscular injection twice daily. This therapy was given in view of the report that parenteral administration of cortisone seemed to improve the possibility of homologous transplantation where the host was not too resistant.[13] Penicillin in one million units six-hourly was given by intramuscular injection.

It was agreed to use a dosage of 700 r whole body radiation using a Picker Vanguard at 280 kV. Initially it was hoped to use single anterior and posterior fields at a focus-skin distance (F.S.D.) of 250 cm. However, the treatment time made this method completely impractical and the following method was employed: 280 kV.; 20 mA.; 145 cm. F.S.D.; H.V.L. 1.7 mm. Cu.; three anterior and three posterior fields 60 x 60 cm.

The field edges were overlapped by 3 cm. to prevent low dosage at the field junctions. This gave 120 r measured dosage at the junctions for 100 r at field centre. A total central body dosage of 683 r with a maximum skin dosage of 830 r (measured dosage) was delivered in a single treatment session on October 28. The calculated planned dosage had been 700 r central body dosage with maximum skin dosage 786 r. All areas were to be bolused to 20 cm. thickness. The actual treatment time was six hours. The total time required to give this six hours of treatment, however, was 13 hours.

Early in treatment after completion of the first field, which was placed over the lower limbs, the patient vomited. Pyridoxine hydrochloride and dimenhydrinate (Dramamine) were given intramuscularly. Vomiting occurred in small quantities on two other occasions but was not a troublesome feature. High fever to 105° F., extreme exhaustion, confusion and restlessness presented the chief problems. Perspiration was excessive. Tepid sponging and intramuscular Sodium Amytal were given.

On the following day, October 29, three sternal marrow aspirations and four left posterior iliac crest aspirations were obtained from the patient's sister. On October 30, three further sternal marrow aspirations and four right posterior iliac crest aspirations were carried out. The marrow was aspirated through a 0.1 mm. steel wire mesh. This material was administered to the patient through a cannula which had been inserted into the saphenous vein at the ankle by "cut down". A 0.01 mm. steel wire mesh screen was introduced between the syringe and the cannula.

Frequent aliquots of the material obtained were counted. A total of 2,905,750,000 nucleated cells were obtained on October 29 in a total quantity of 113.5 c.c. and 1,164,700,000 nucleated cells were obtained in 46.5 c.c. on October 30. The total number of nucleated cells injected was therefore 4,070,450,000.

The patient's blood group was A, Rh positive—CDe/cDE. The patient's sister was group A, Rh positive—CDe/cde. The blood of the donor was crossmatched with that of the recipient and was shown to be compatible.

On the day following irradiation, the patient's blood urea was 110 mg. %. It was thought that the electrolytic disturbance was caused by salt depletion. The patient had taken nothing by mouth and had shown a tendency to sweat excessively. With appropriate electrolyte management his blood urea fell to 42 mg. % by November 2, and the serum electrolytes were normal.

Details of the hæmatological findings after treatment are recorded in Table I. On each day from October 30 until November 3, no reticulocytes were found in the peripheral blood. No polymorphonuclear leukocytes of female type were identified.

Before receiving the radiation, the patient had been running an irregular pyrexia which had varied between 98° and 101° F. This fever continued after treatment at a similar level but on November 3, shortly before his death, it again rose to 105° F.

TABLE I.

Date	*Hæmoglobin*	*White blood count*	*Platelets*	*Reticulocytes*	*Polys.*	*Juvenile forms*	*Lymphocytes*
October 30	5.5 g.% (38%)	2800/c.mm.	7000/c.mm.	0	12%	8%	80%
October 31	4.8 g.% (31%)	1200/c.mm.	6600/c.mm.	0	34%	4%	62%
November 1	5.5 g.% (35%)	900/c.mm.	10,300/c.mm.	0	6%	1%	88%
November 2	6.6 g.% (42%)	800/c.mm.	7000/c.mm.	0	0	0	100%
November 3	7.4 g.% (47%)	900/c.mm.	7560/c.mm.	0	0	0	100%

AUTOPSY FINDINGS

On November 3 at 6:30 p.m.—55 minutes after death—an autopsy examination was performed by Dr. J. W. Whittick. Examination of the head and neck revealed enlargement of lymph nodes in all cervical groups. The paratracheal, bronchial and axillary lymph nodes were also enlarged. Most marked lymph node enlargement was present in the cœliac, hepatic, portal and paraaortic groups. The glands were soft, mobile and œdematous.

Microscopically, all these nodes were similar in structure. Follicles were lost and there was diffuse but loose replacement by cells mainly lymphoblastic in type. Degeneration and fine necrosis of these cells was present.

Reddish fluid was present in both pleural sacs. Fibrous adhesions bound both lobes of the left lung to the posterior chest wall. Acute fibrinous pleurisy was scattered in small patches on the surfaces of both lungs. Numerous petechiæ were present on both the parietal and visceral pleura. There were several circumscribed, raised, dark red areas on the surface of the lungs, particularly the right. Both lungs showed congestion, extensive hæmorrhages and poorly defined greyish areas of induration. No thrombi could be recognized. Œdema was present in both lungs and was particularly profuse in the left. Some œdema was also present in the mediastinal connective tissues.

On microscopic examination, there were areas of recent hæmorrhagic infarction with deposits of fibrin on the overlying pleura. Elsewhere there was œdema and hæmorrhage. Hyaline thrombi filled some alveolar vessels, and a common finding in all the lung sections was focal thickening of alveolar walls. No erythropoietic or granulopoietic cells were identifiable in the lungs. Fat staining of an infarcted part of the lung showed fine fat droplets, mainly within the cytoplasm of the histiocytes. Larger fat droplets were present in alveolar capillaries in a non-consolidated area.

Small petechiæ were scattered fairly profusely through the gastric musosa except along the lesser curvature. Very few mucosal petechiæ were present in the small intestine, while in the large intestine they were almost entirely confined to the transverse and pelvic colon.

There was great enlargement of the liver (2968 g.), which showed diffuse, linear and stellate opacities of its capsule superiorly and anteriorly. Great enlargement of the spleen (940 g.) was also present. Its cut surfaces were firm, with only fine trabeculæ recognizable in its smooth, dark red pulp.

The adrenals were very small (left—4.6 g., right—4.2 g.) and had pale yellow cortices. The medullary substance appeared to be normal in amount. The kidneys, bladder and prostate were normal.

There was pronounced œdema of the retroperitoneal connective tissues over the posterior abdominal wall. This œdema was similar to that in the mediastinal connective tissue.

Soft, pale brown, œdematous marrow was abundant in the sternum. Marrow in the ribs was similar in appearance. That in the upper third of the femur was paler and more gelatinous, while marrow in the distal third of the same femur was clear, pale, green and gelatinous.

Microscopic examination of the bone marrow from the lumbovertebral bodies, ribs, sternum and femur revealed that lymphoid cells—lymphocytes and forms intermediate between lymphoblasts and lymphocytes—formed the bulk of the cells present. Cells of the granulocytic series were represented by an occasional eosinophil. No erythropoiesis was identifiable. The megakaryocytes had pyknotic, distorted nuclei and were necrotic. Six thousand nucleated cells were observed without encountering a single polymorphonuclear leukocyte.

DISCUSSION

With existing methods of treatment, a diagnosis of leukæmia, acute or chronic, carries with it the certainty of a fatal termination. Conventional radiotherapy and chemotherapeutic agents will help to make the remaining months or years of life more comfortable and may prolong the period of survival, but the time comes when none of these agents will alter the course of this disease. It seemed justifiable, therefore, to attempt whole body radiation with subsequent marrow transfusions in a patient who had reached a terminal stage of chronic lymphatic leukæmia.

Unfortunately, the adaptation of a successful laboratory procedure with experimental animals to a clinical procedure with man raises many problems. The LD50 for inbred laboratory animals can be established. The LD50 for man is not known but information from bomb disasters and accidental exposures suggests that it is in the neighbourhood of 300-450 r.

Assuming that the lethal dose of whole body radiation for man has been established, the method of delivering it to an acutely ill patient presents

many technical difficulties. Even if these difficulties are surmounted, one must then pause to give thought to the outcome if the procedure proves successful and the patient survives. What will be the condition of the skin, eyes, endocrine system and viscera? If a total body radiation and marrow transfusions result in a successful marrow take, will the patient die from radiation damage to the tissues without any intervening period of comfortable life? Will a delayed immunological response of the host to the injected bone marrow prove fatal? The answers to these questions with regard to man are not known.

Although it is obviously dangerous to draw conclusions from one patient, it is possible to make several observations which were true for this patient, although they may not be true for others. In spite of the large dose of radiation given, primitive, immature cells were still present in the peripheral circulation and the marrow still contained abundant lymphocytic material at the time of death. Despite careful searching absolutely no evidence of a marrow "take" was found.

The evidence suggests that the treatment was a complete failure. If the results of animal experiments are applicable to man, some donor cells should have been present in the recipient's bone marrow five days after injection.[6] Merwin and Congdon found homologous cells in the marrow of irradiated treated mice on the day of injection and these homologous cells increased markedly in 12 to 14 days. These findings also agree with observations of Nowell *et al.*[5]

Thomas *et al.*[11] used minor differences in the CDE grouping in an attempt to determine whether a marrow repopulation had occurred. It was thought by us that these minor differences might be more significant from an immunological point of view, and therefore we chose the patient's sister and relied on nuclear sexing for recognition of the donated cells. In the series reported by Thomas *et al.*,[11] of a total of three patients given whole body radiation and bone marrow, there was suggestive evidence of a temporary "take" in two patients. There was no pulmonary embolism present in these patients.

With regard to the amount of bone marrow injected, it was found that the peripheral leukocyte count and the spleen weight in irradiated mice showed very quick recovery with massive doses of bone marrow.[14] For both end points, an optimum response was reached. Thomas *et al.*,[11] in considering the amount of bone marrow needed to produce repopulation of the marrow spaces of adult man after lethal radiation, based their calculations on the fact that 1,000,000 to 10,000,000 nucleated cells is an effective dose for a 30-gram mouse[15] and 200,000,000 to 2,000,000,000 for a 3-kg. monkey.[9, 14, 16] It was suggested that 4,000,000,000 to 40,000,000,000 nucleated marrow cells of the usual differential distribution might be expected to be a significant and effective dose in man.[11] The number of nucleated marrow cells injected in this patient (4,070,450,000) is just within this range.

In considering the possible explanation of failure of this form of treatment in this patient, it is well to remember that the chances of obtaining a successful marrow transplantation with isologous material are much higher than with homologous, and these in turn are higher than with heterologous material. Most of the work in this field has been done with highly inbred strains of animals. Man is undoubtedly homologous and it is difficult to know how much of the experimental findings are applicable. Work using wild mice in whole body radiation and marrow transplantation experiments does not seem to have been done.

We have attempted to list the possible causes of failure of injected bone marrow to repopulate the marrow spaces in a human being exposed to whole body radiation. These possible causes can conveniently be divided into two groups, the first fundamental to the procedure itself and the second due to errors in technique. In the former group, there may be host rejection of donor marrow. It may be that injected bone marrow will not repopulate the marrow spaces in man following whole body radiation, and that the successful results obtained in animals are not reproducible in man. The hæmopoietic system in animals and man may be different, and what may be applicable to disease and therapy in one is not in the other. With regard to errors in technique, the dosage of whole body radiation may be too great or too small. The amount of bone marrow injected may be insufficient. There may be a failure of donor marrow to pass the lung barrier in man. The patient's general condition may be so poor and his condition so terminal that he is unable to tolerate the procedure.

Humble and Newton[18] injected bone marrow intra-arterially into four patients. They did not use radiation. This technique would be expected to reduce greatly the hazard of pulmonary embolism and, although systemic vascular obstruction might be expected to occur, they did not encounter it. One patient died after percutaneous aortic puncture.

In future application of this technique, an attempt should certainly be made to remove the fat from the bone marrow before it is injected into the recipient. This procedure, although it involves a manipulation *in vitro*, is obviously necessary to prevent fat embolism, as was found in the patient under present consideration. The use of the 0.1 and 0.01 mm. wire mesh screen did not seem to be entirely satisfactory. The fat could be removed by centrifugation. We have found in subsequent experiments that it is much easier to remove the fat-free marrow from beneath the supernatant fluid, as removal of the supernatant fluid and subsequent recentrifugation tended to leave deposits of fat on the sides of the test tube.

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We think that attempts to increase the cellularity of the donor's marrow by bleeding or by the use of phenylhydrazine are probably not indicated, as it seems most unlikely that these procedures would increase the number of stem cells present. While conjectural, it would seem most probable that it is the stem cell which is the fundamental entity in any successful repopulation.

SUMMARY

An unsuccessful attempt at homotransplantation of marrow after whole body radiation in a patient suffering from terminal lymphatic leukæmia is reported. The reasons for failure and possible improvements in technique for the future are discussed.

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A CASE OF MARFAN'S SYNDROME WITH AN ANEURYSM AT THE ASCENDING AORTA WITH PHYSIOLOGIC, OPERATIVE AND POSTMORTEM STUDIES*

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SINCE 1943, there have been a number of reports in the literature dealing with cystic medial necrosis of the aorta in Marfan's syndrome; those afflicted have died either in congestive failure or from dissecting aneurysm of the aorta. The following case is presented because it illustrates the fact that with modern investigative techniques, it is possible to make a definite diagnosis of this condition during life, and because recent advances in the surgery of aortic aneurysm may now hold out some hope for these patients.

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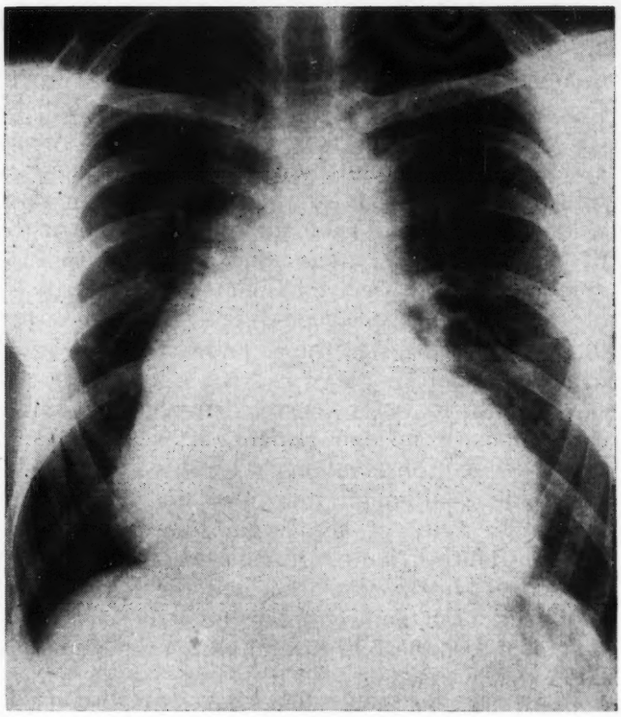

Fig. 1

The patient, a 30-year-old single white man, was admitted to hospital with a history of progressive dyspnœa of eight months' duration. During the summer of 1956, he suffered with severe sore throat and was told at that time that he had heart trouble. About the end of the year, his breathlessness became more noticeable but he carried on with his work as a farmer until one week before admission to the University Hospital.

There had been no past illness of note. As a child, he had spent some time in hospital for repair of congenitally deformed fingers. The patient's only brother was believed to be in good health at the time of his death in an air crash.

The patient was a slim, mildly dyspnœic man with a narrow head and a highly arched palate. The fingers were tapering and showed contractures, and there was a bilateral pes cavus. There were grossly distended pulsating veins on the right side of the neck, and each heart beat caused a heaving of the front of the chest, and shook his body. Pulse was 100 per minute, regular and collapsing. There was capillary pulsation. The pupils were equal and the fundi normal. There was a diastolic thrill palpable to the right of the sternum. The heart was enlarged, mainly to the right, the left border to the midclavicular line and the right border beyond the midclavicular line. On auscultation, a diastolic murmur was heard all over the precordium, maximal over the base of the heart. The blood pressure was 140/35 mm. Hg. The lungs were clear. Examination of the abdomen was negative. There was no peripheral œdema. Examination of the nervous system revealed no abnormality.

INVESTIGATIONS

Blood: Hb. 14 g. %, white blood cells 9550/c.mm. with a normal differential count, sedimentation rate 6 mm./1 hr.

Urinalysis: negative.

Venous pressure: 15 cm. saline (zero level 10 cm. from back).

Circulation time: arm to tongue: 35 sec. (Decholin); arm to lung: 19 sec. (ether).

Wassermann: negative.

E.C.G.: showed sinus rhythm and left heart strain.

Fluoroscopy (Fig. 1): The heart was greatly enlarged and this involved both the right and left ventricles. There was gross dilatation of the ascending aorta, which showed vigorous pulsations. Lung vascularity was normal.

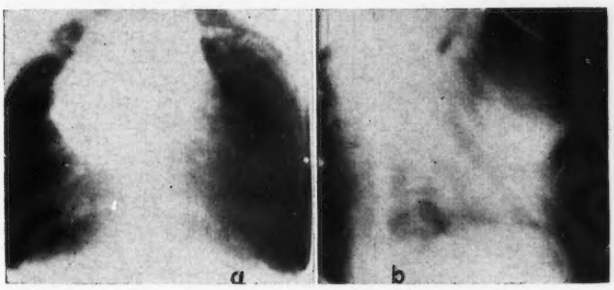

Fig. 2a and 2b

Right heart catheterization and retrograde aortogram.—It was thought that he might have ruptured a sinus of Valsalva into the right atrium, and on March 6 these procedures were carried out. The blood samples from the right side of the heart and pulmonary artery did not show evidence of arterialization, and it was decided to proceed with the retrograde aortogram. The left brachial artery was isolated under Xylocaine (lidocaine) anæsthesia and a No. 8 Lehman angio-catheter was introduced into the artery.

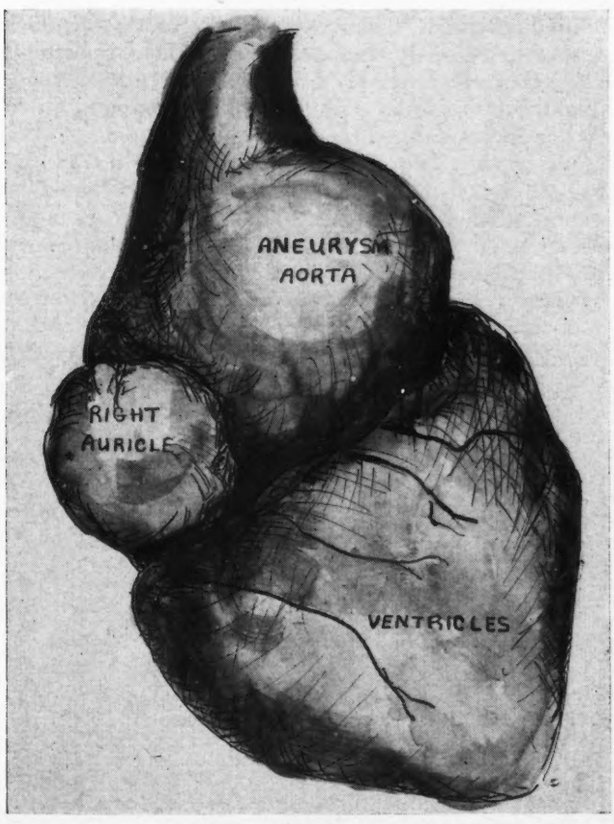

Fig. 3

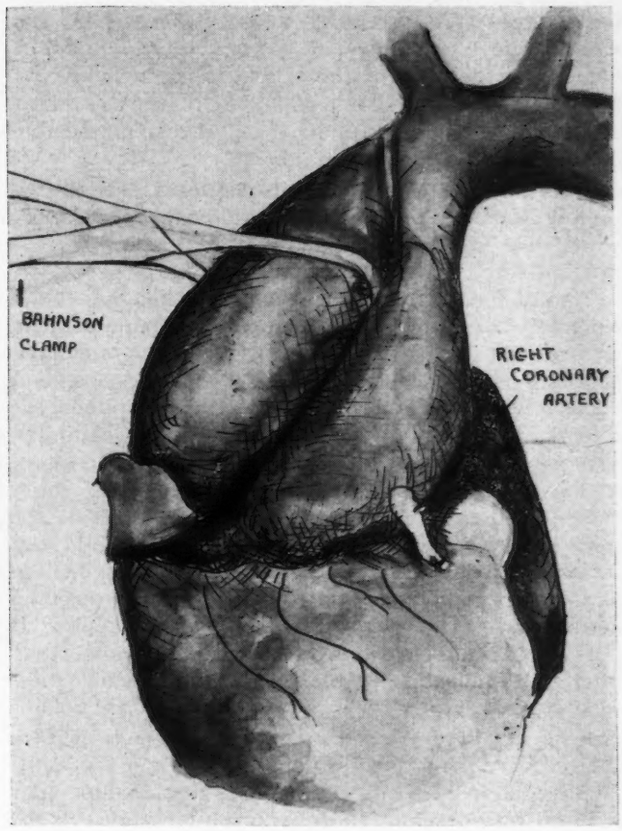

Fig. 4

Under fluoroscopic control the tip was advanced towards the heart and was positioned in the ascending aorta about 3 cm. above the aortic valve. After a test dose, 25 c.c of 70% Diodrast (iodopyracet) was then in-

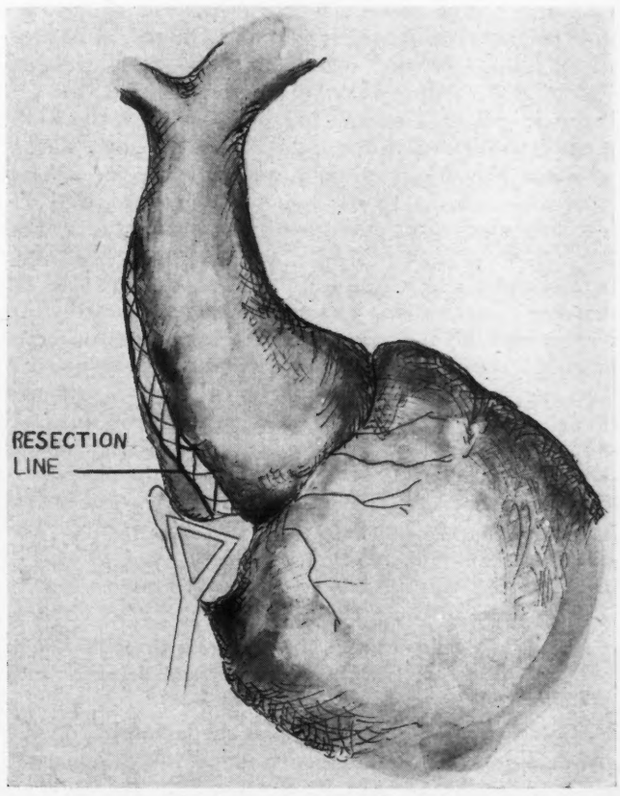

Fig. 5

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jected over three seconds, and 17 films (PA and lateral) were obtained at 2 per second, with a Schonander Bi-plane machine. The aortogram (Fig. 2a, 2b) showed a very large dilatation of the ascending aorta. This aneurysm appeared to arise from the root of the aorta.

Over the next two weeks, his condition deteriorated rapidly and he developed severe congestive failure which was unresponsive to medical treatment. As a last measure, it was decided to attempt a partial resection of the aneurysm. On March 22, bilateral thoracotomy was performed. A moderate amount of fluid was present in both pleural cavities and in the pericardium. There was a huge heart with enlargement of all chambers and gross enlargement of the pulmonary artery. The aneurysm of the ascending aorta (Fig. 3), approximately 6 cm. in diameter, extended right down to the sinuses of Valsalva. The right coronary artery came off the aneurysm just above the edge of the right ventricle. The left coronary artery could not be seen. The Bahnson clamp having been applied so as to remove about one-third of the dilated ascending aorta (Fig. 4), the resection was taken as near as possible to the root of the vessel (Fig. 5). Immediately after the application of the clamp, the diastolic pressure increased from 50 to 70 mm. Hg.

After the operation, the patient was returned to the recovery room and his general condition was satisfactory. Some 12 hours later, and a few minutes after he had been talking to the nurse, he said that he felt short of breath, and died suddenly.

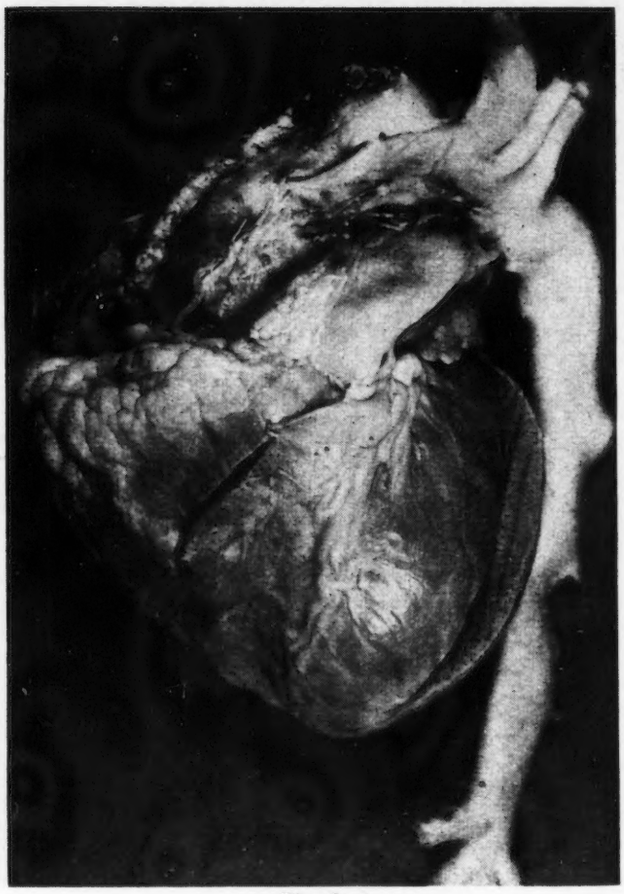

Fig. 6

POSTMORTEM FINDINGS

The body was as described in the physical examination.

Thoracic cavity.—An opening had been left in the pericardium which contained approximately 1000 c.c. of fluid and clotted blood. The right and left pleural cavities contained respectively 250 and 100 c.c. of hæmorrhagic fluid. The heart, together with the aorta, weighed 720 g. Both ventricles were greatly enlarged, the left ventricle being 1.8 cm. in thickness and the right 1 cm. The incision in the right side of the aorta started at about the origin of the right coronary artery and extended upwards to the innominate vessel (Fig. 6). The ascending aorta was greatly dilated and measured 4.9 cm. in diameter. There was enormous dilatation of the aortic sinuses of Valsalva and the diameter at this level was 5.9 cm. The aortic ring and aortic cusps were stretched. Both coronary arteries rose at a higher level than usual; they were soft and widely patent. The medial aspect of the right auricular wall adjacent to the recently resected aortic aneurysm was thin and in the ascending aorta there was an annular, irregularly outlined zone of 3.0 cm. maximum width which was denuded of intima. The entire wall of the aorta in this situation was thickened, œdematous and friable. The media in the remainder of the aorta was unusually thin and the intimal surface displayed multiple tiny atheromatous plaques.

Kidneys.—A horseshoe kidney was present which weighed 300 g. The capsules were stripped with difficulty.

Microscopy: heart.—There was hypertrophy of the myocardium and moderate degrees of arteriosclerosis, perivascular fibrosis and patchy fatty degeneration of the muscle fibres. There was thrombotic material in the right auricular appendage, which was of recent antemortem formation.

Aorta (Figs. 7 and 8).—Sections from the aneurysmal segment showed marked degenerative changes of medionecrosis. The elastic fibres and the finer lamellæ had largely disappeared and those remaining were coarse, fragmented and frequently widely separated by acellular pale basophilic substance. There was an increase in, and patchy hyalinization of, the fibrous connective tissue, especially in the adventitia. Multiple areas on the inner surface were denuded of intima and these ulcerative lesions had often extended to the inner media. The arch and descending aorta exhibited only minimal degeneration.

Pituitary was not remarkable.

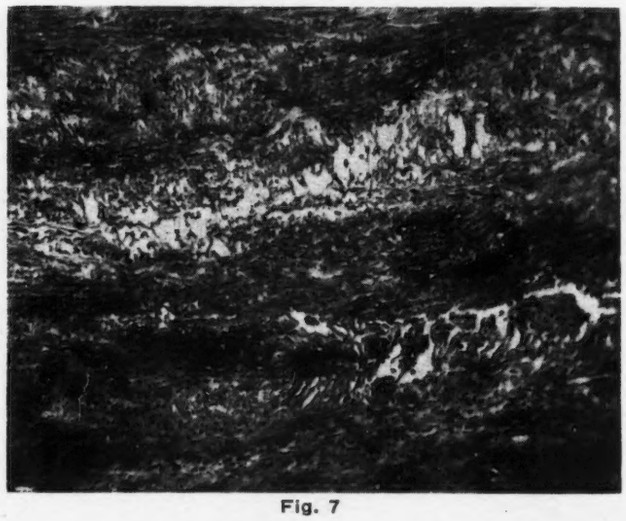

Fig. 7

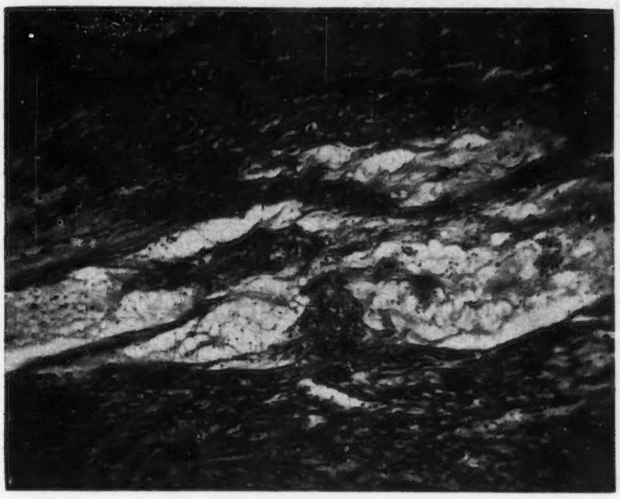

Fig. 8

DISCUSSION

It was suggested by Weber[1] that the name "Marfan's syndrome" be retained for this condition, as the fingers may not be unduly long. This was so in our case. Morever, it is preferable to "arachnodactyly" as it serves nowadays to focus attention on the visceral abnormalities in spite of the fact that the original paper was concerned almost entirely with skeletal changes.[2] Baer, Taussig and Oppenheimer[3] were the first to describe two cases of this syndrome with an aneurysm of the proximal part of the aorta. They described the malformation of the media, but sought to distinguish it on histological grounds from the *medionecrosis aortæ idiopathica* of Erdheim.[4] Other authors (Tobin,[5] Goyette and Palmer[6]) maintained that the aortic lesions in these cases are indistinguishable from the condition described by Erdheim, and we are in agreement with this.

In his comprehensive review of the subject, Rados[7] raised the question of etiology and suggests that it is essentially an aberration of the anlage. McKusick[8] studied 50 families and is of the opinion that clinically Marfan's disease behaves as an abiotrophy of some connective tissue element, while Dent[9] goes still further and believes that this, like all hereditary diseases, is due basically to a biochemical disorder.

When skeletal, ocular and cardiac abnormalities are all present, there is no difficulty in diagnosis, as pointed out by Goyette *et al.*; however, in those cases presenting only a few features of the complete syndrome, it may be overlooked. An aneurysm in a young adult may represent a "forme fruste" as, for instance, in the case reported by Davies.[10]

The diagnosis of congenital aneurysmal dilatation of the ascending aorta was entertained during life in the case of Schorr[11] on the basis of clinical and angiocardiographic observations. Bahnson and Nelson[12] reported five cases of cystic medionecrosis of the aorta treated surgically. They had one patient with Marfan's syndrome who was operated on unsuccessfully, and they mention that in Marfan's syndrome the immediate beginning of the aorta, and especially the sinuses of Valsalva, seems to be most severely affected.

We concur with their statement that the results of surgical treatment require further investigation.

SUMMARY

A case of Marfan's disease is described in which the diagnosis of aneurysm of the ascending aorta was established during life. An attempt was made to treat the condition surgically, but the patient died 12 hours after completion of the operation.

Postmortem findings, including histology, are given and the literature is briefly discussed.

Our thanks are due to Dr. I. M. Hilliard for permission to publish this case and to Dr. D. Moore for histological reports.

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THE BACTERIOLOGY OF TUBERCULOUS LESIONS RESECTED AFTER CHEMOTHERAPY

In an investigation by Bloch *et al.* (*Am. Rev. Tuberc.*, 77: 245, 1958), 400 open and closed tuberculous lesions of all sizes obtained by resectional surgery were studied bacteriologically, both by direct microscopic examination and by culture. The essential results were those obtained by culture. The majority of all lesions, even of the small closed ones, were found to contain caseous material. The small closed foci which constituted nearly one-third of the entire material were considered a feature of special interest. Whether a cavity contained tubercle bacilli depended to some extent upon its size, the largest ones yielding the greatest number of "positive" cultures. In the closed lesions, size was of no significant influence.

Slightly more than one-third of all patients had preoperative sputum "conversion," but in 35.7% of them one or more lesions in the resected specimen were positive for tubercle bacilli on microscopy and culture. The percentage of patients with preoperative sputum "conversion" was smallest in the group in which the specimen was "positive" both on microscopy and culture. The status of the sputum with respect to tubercle bacilli before the beginning of chemotherapy furnishes a good forecast of bacteriologic findings in the specimen. The duration of preoperative antimicrobial therapy had a great influence on the cultural response of resected lesions. In both open cavities and closed foci, progressive bacterial resistance under prolonged treatment resulted in a greater number of cultures from the specimen which were positive for tubercle bacilli. The crucial period seems to lie between six and 12 months.

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The Canadian Medical Association Journal

published twice a month by
THE CANADIAN MEDICAL ASSOCIATION
Editor: S. S. B. GILDER, T.D., M.B., B.Sc.
Managing Editor: T. C. ROUTLEY, M.D., F.R.C.P.[C.]
Assistant Editor: M. R. DUFRESNE, M.D.
Editorial Offices: 150 ST. GEORGE ST., TORONTO
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DOCTORS ON TELEVISION

In our last issue we commented on the relationship between medicine and the mass media of communication, noting the varying degrees to which the organized medical profession collaborated with these media in different countries and pointing out the unfortunate relationship which had developed between our colleagues in the United Kingdom and the television services of the British Broadcasting Corporation. In direct contrast to this, the April issue of *PR Doctor,* issued by the Public Relations Department of the American Medical Association, contains evidence that organized medicine in the United States is eager to have physicians take advantage of the educational facilities offered by television programs.

The entire issue of *PR Doctor* is devoted to consideration of television, beginning with emphasis on the great dramatic value of medicine and the great public interest in matters medical.

Even a small amount of observation will bear out amply the great concern of the United States public with their bodies and their minds. Every corner drug store contains an assorted collection of paper-back fiction of varying degrees of badness, dealing with the glamorous and dramatic lives of medical colleagues, such as most of us have never encountered. To this may be added the vast number of popular accounts of medical conditions, and the pathetic biographies of courageous sufferers from a variety of diseases.

It is always difficult to draw the line between serious art and pornography, and it is equally difficult to determine when intelligent interest becomes morbid curiosity. It is perhaps only fair, however, to add that those who control the radio, TV and newspapers are most circumspect in observing the proprieties; for example, none of the patients appearing in these media ever seem to suffer from disorders of the genito-urinary system or the lower bowel.

Granted, however, that the public is determined to find out what makes itself tick, the American Medical Association is undoubtedly right in urging medical societies to take the lead in fulfilling this widespread want. Letters of gratitude from listeners or viewers have suggested to medical societies that television programs they have arranged have indeed proved helpful to patients, and have enabled them to see the point of view of the physician, as well as giving them some insight into the details of medical economics.

The suggestion that physicians identified by name and appearing in television programs may receive undesirable publicity is counteracted by the statement of one physician with an eight years' record of broadcasting, who claims that only six listeners have ever requested appointments with him as a direct result of hearing his program. He explains that most viewers project their own family physician into the role of the TV doctor.

While there can be little disagreement on the value of programs covering preventive medicine, many Canadian physicians may not be too impressed with the statement that "live telecasts of surgery hold more people to their TV sets than the most spine-tingling drama". One state medical society seems to have found the effort of televising a live operation worthwhile. The society thought of all the possible difficulties which could arise during the telecast, such as the death of the patient on the table, making a mistake in full view of the audience, or the finding of a much graver condition than had been suspected. They arranged a panel discussion which could be switched on instead of the telecast if anything went wrong, and selected their patient with great care. Presumably the patient was as satisfied with the result as the medical society was.

Physicians in the United States are of course faced with one problem which does not arise here, that is, the problem of program sponsorship. We are told that the American Medical Association in its telecasts sticks to programs with institutional sponsorship. Lastly, it is worth noting that the American Medical Association has had in operation for nearly two years a Physicians Advisory Committee on Television, Radio and Motion Pictures. This committee, which consists of two groups, one in Los Angeles and one in New York, composed of volunteer physicians representing various specialties, checks TV scripts for medical accuracy. Its policy of "help not yelp" is said to have ensured its widespread use by TV producers across the United States.

Editorial Comments

SEIZURES AND SYNCOPE

The close relation between epileptic seizures and vasodepressor syncope has long been recognized and is succinctly expressed in the maxim, attributed to Gowers, that anyone who faints often enough will sooner or later have a fit.

Recent discussions[1] of this diagnostic problem have emphasized the occurrence in syncope of features—involuntary movements of the arms, occasional incontinence of urine—that have long been held to be characteristic of epilepsy. Indeed cerebral ischæmia, the cause of unconsciousness in syncope, may itself result in an epileptic seizure. The difficulty of this differential diagnosis in doubtful cases has to some extent been increased by this blurring of outlines, but the decision is of the greatest importance for the patient and is a constantly recurring problem for the physician.

The criteria upon which the diagnosis is reached are implicit in the definitions of vasodepressor syncope as resulting from cerebral ischæmia, and of epilepsy as due to "occasional, sudden, excessive, rapid and local discharges of grey matter".[2]

If the attack is witnessed or reliable information about the state of the pulse and blood pressure during the attack is available, the diagnosis is usually easy. As a rule such information is missing and the diagnosis must often rest upon the history. The fundamental points are the presence of a cause, the relation to posture and the characteristic sequence of events at the onset of and during recovery from syncope. The epileptic attack is usually causeless, is unrelated to posture, is abrupt in onset, and is commonly followed by a short-lived confusional state. A further characteristic of epilepsy is its focal origin, whether from the central grey matter or elsewhere, and the search for evidence of a local origin for the discharges is an important part of history-taking in these cases.

The detail of the attack, as indicated above, is evidence of lesser value, but the repeated occurrence of attacks of identical pattern, of repeated incontinence of urine and of tonic spasm of the legs are all strongly suggestive of epilepsy. Physical examination may make the diagnosis clear but usually does not, and the electroencephalographer is often called upon for help in borderline cases.

A number of studies have been devoted to an attempt to define the value of the E.E.G. in solving this problem. In a recent paper,[3] 18 patients with typical syncope were studied. Of five with organic disease that might have caused this symptom three had abnormal resting E.E.G. records. Of the 13 other cases, one had an abnormal resting record. The abnormalities described were bursts of "prominent sharp activity and fast activity", "slowing on hyperventilation" and "bursts of paroxysmal activity"—all relatively non-specific abnormalities.

This and many other papers emphasize both the limitations and the value of the electroencephalogram in these cases. Hill[4] has stressed that one normal E.E.G. record is evidence neither for nor against epilepsy and that non-specific abnormalities may be seen in the records of normal people, of epileptics, of those with organic nervous disease, of psychotics and of psychopaths. The presence of epileptic discharges does not mean that the patient cannot have fainted. In short, the question of the nature of a patient's symptoms is one that should be answered by the clinician. In this task, the evidence provided by the E.E.G. is of varying value and must be assessed together with the clinical and other evidence. It must be emphasized that the presence of bilaterally synchronous and symmetrical bursts of slow activity is very strong evidence that the patient suffers from epilepsy and should lead to careful reassessment of the history, if the diagnosis of syncope has been made. Failure to demonstrate an expected focus on a routine E.E.G. does not invalidate a diagnosis of epilepsy, and the significance of its demonstration depends, as with other E.E.G. findings, on the circumstances of the case. Finally, the E.E.G. may demonstrate the existence of a pathological process in the brain, and Hill (*loc. cit.*) considers that this is its major value in such cases.

R. A. CHAMBERS

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NATURAL HISTORY OF HEART BLOCK

Our understanding of heart block is frequently restricted and circumscribed by the fact that the average cardiologist usually sees cases of this conduction disturbance from one of two points of view. In some instances, he may never see the patient at all, and the case presents itself to him in the form of an electrocardiogram to be interpreted in the course of his daily duties. In other circumstances, the situation is one of Adams-Stokes syncope, in which the heart block is fully established or alternates between a partial and a complete conduction defect.

In a long and varied experience in cardiology, one may, however, have the opportunity of following up a relatively large number of examples of this condition from their early phases to their ultimate conclusions; and, if adequate records are kept, one may accumulate data on a fairly large number of patients, with the aid of which the natural history of this condition can be thoroughly worked out.

A study of this type has recently been reported by Gilchrist[1] from the Department of Cardiology of the Royal Infirmary, Edinburgh, which has provided us with a more or less connected story of the development of various degrees of heart block, has clarified several interesting and important questions that have long been vexing cardiologists, has raised certain other ones that now require answers, and has most certainly emphasized the role of physical examination in the diagnosis of this conduction defect.

Some of the questions answered in this thoughtful and scholarly study are: What is the explanation for the fact that the severest grades of partial heart block, taking a chronic or subacute course,

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are less frequently encountered in clinical practice than complete block? Does complete block more often arise abruptly than with premonitory indications of partial failure of the link uniting atria and ventricles? Are there ever reliable clinical clues that may arouse in the mind of the physician the thought that heart block is probably present or that complete and permanent block may develop in a patient at some future date? If so, what can be done to avoid or postpone such an eventuality? How often is complete block a manifestation of a reversible process? With atrioventricular conduction restored in full, how great is the tendency to repeated relapse with the production of recurrent bouts of complete block?

It would appear that high degrees of heart block falling short of the complete form are much less prone to cause symptoms than is complete block. Generally speaking, we associate Adams-Stokes syncope with complete block rather than the partial form; when such attacks occur, they undoubtedly call attention to the presence of the complete conduction defect, if it exists. However, Gilchrist points out that fainting attacks, similar to Adams-Stokes syncope, can occur in the presence of high-grade partial block, and are not exclusively the property of complete block; and there is an impressive body of evidence which indicates that attacks of syncope are commonest *not* when an idioventricular rhythm has been established but during the short periods of asystole that occur during the transition between partial and complete block.

The three grades of defective atrioventricular conduction commonly described are as follows:

First-degree block—commonly the result of digitalis therapy, and marked by a lengthening of the P-R interval beyond 0.20 second.

Second-degree block: Type I consists in progressive lengthening of successive P-R intervals leading to single ventricular beat omissions (i.e. Wenckebach periods); Type II shows abrupt rhythmic omission of ventricular beats in regular sequence *without* lengthening of P-R intervals, e.g. atrioventricular ratio commonly 2:1 or 3:1 or rarely 4:1.

Complete A-V block: otherwise known as complete heart block or atrioventricular dissociation. In this condition the atrial and ventricular rhythms are independent, either with or without associated syncopal attacks (Stokes-Adams seizures).

The point is made that clinical methods can be used to provide reliable clues to impaired atrioventricular conduction. For example, the distinctive peculiarity is that the first heart sound at the apex varies in quality and in intensity from cycle to cycle. In certain single cycles a grossly accentuated first sound—the so-called "bruit de canon"—occurs. This variation in intensity of the first sound at the apex is due to the constantly changing time-relationship between the atrial and ventricular contractions. For example, if the ventricle contracts very soon after the atrium, the valve leaflets, which are then hanging low and relaxed, are thrown violently back and snapped together in the closed position. This creates a loud first sound—the "bruit de canon". If, on the other hand, a very long time interval separates successive atrial and ventricular systoles, then the leaflets, floating up on the blood distending the ventricular cavity, have only a short distance to travel when systole occurs. In these circumstances, the first sound may be very faint and soft. All intermediate gradations may occur. It is easily understandable, also, that if an apical systolic murmur is present it will also be altered in character and intensity, again depending on the changing time-relationships between the atrial and ventricular contractions.

When the ventricles are beating slowly, an atrial contraction occurring early in ventricular diastole—that is, during the period of rapid ventricular filling—may be sufficiently intense to produce a mitral diastolic murmur. In some cases, also, during long periods of ventricular asystole, careful auscultation may reveal a regular succession of audible atrial contractions. In contradistinction to the "bruit de canon", under such circumstances the first heart sound may be very faint. Naturally, bradycardia is a common finding in all types of high-grade heart block, and the diagnosis can always be made by electrocardiography.

By clinical methods, it is also possible to distinguish between Type I and Type II 2:1 block. In Type I partial block, but not in Type II, the Wenckebach phenomenon is in evidence. Thus, a simple test with exercise or atropine, both of which increase the atrial rate—followed by electrocardiography—will reveal a reduction in the degree of block in Type I, and an increase in the degree of block in Type II. This, of course, is the result of the flexibility of the P-R interval in Type I block and its rigidity in Type II.

So far as one can determine, there appears to be no method of avoiding or postponing the development of complete block in a patient who already suffers from the partial conduction defect. It is possible to state only that progression from partial to complete block may take one of two courses. In the first form, the attacks of complete block occur sporadically, at long intervals and by direct progression from regular sinus rhythm. In other words, the cardiac mechanism may be proceeding normally at a regular rhythm, when it is suddenly interrupted by an episode of complete heart block, with Adams-Stokes syncope. Reversion to a normal rhythm is equally sudden and unpredictable. This may be designated as paroxysmal complete atrioventricular block. In the other form, the patient suffers from high-grade Type II block, and this rhythm occasionally, and with greater or lesser frequency, gives way to spells of complete block. Adams-Stokes seizures are not necessarily an accompaniment of these changes of rhythm, although they may occur. However, the final situation is the same—that is, complete atrioventricular block, which ultimately becomes established as a permanent entity. It should be emphasized that Adams-Stokes attacks are much less frequent during the second type of progression than during the first, although exceptions frequently occur.

It must not be supposed that these are the only two sequences of events whereby complete heart block may eventuate. Complete heart block may develop as an acute episode, specifically during acute myocardial infarction. This, of course, may

be due to temporary or transient œdema of the tissues surrounding the atrioventricular node or bundle, or may be the result of actual infarction of the conducting tract. In the one case, as indicated, the complete heart block may be temporary and reversible, while in the latter case the acute development of complete heart block may be an irreversible phenomenon.

In contradistinction to acute complete block, usually resulting from a myocardial infarction, chronic complete block may occur *de novo*. So far as is known at present, a gradual progression to complete block in these cases cannot be excluded, since they may be first seen by a physician only after complete block has developed. However, such a situation may result from congenital heart disease, coronary atherosclerosis without myocardial infarction, endocardial fibroelastosis, and rheumatic or other forms of myocarditis.

Surprisingly enough, cases are on record (some are quoted by Gilchrist) in which recovery from chronic complete block has taken place and is well documented. No satisfactory explanation can be offered for this sequence of events, but it is suggested that in these cases the independence of atrial and ventricular activity results not from a structural lesion, congenital or acquired, but from a more subtle functional state, attributable perhaps to an electrolyte disturbance or a biochemical or toxic derangement, interfering with the spread of the impulse through the atrioventricular node and bundle, although the conducting tract itself may be structurally intact.

Finally, about 7% of cases of high-grade heart block fall into a miscellaneous group, usually of a temporary nature, and associated either with drug intoxication or a hypersensitive carotid sinus mechanism. The drugs responsible are usually either quinidine or digitalis, and improvement may result from large intravenous doses of atropine.

It is abundantly clear from this study that the subject of heart block is a highly complex one. However, by careful study of individual cases, clinically, pharmacologically, and electrocardiographically, one may frequently bring a semblance of order out of what might otherwise be dismissed as complete chaos.

S. J. SHANE

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EPIDEMIOLOGICAL STUDIES OF THE ELDERLY MALE

The Social Medicine Department of Birmingham University, England, analyzed the records of over 1000 men aged 60-69 kept by 11 general practitioners in their area.[1] Some of their findings (previously reported) concerned the relationship between the incidence of coronary artery disease and the social class of the men. They may be summarized by saying that coronary disease was found to be commonest in men in sedentary occupations, and myocardial infarction commonest in social class I (professional).

The main purpose of the present inquiry was to establish the incidence of clinically significant disease, its variations according to social class, and the incidence of disability and unfitness for full-time employment. Although it was found that four of every five men in this age group had clinically significant disease, this was causing some degree of disability in only half the cases. The incidence of disease and disability increased after the age of 65 and rose sharply as the 69th year was approached. Except for the coronary artery disease mentioned above, the incidence of disease and disability was much higher in the lower social classes. As regards fitness for employment, it was found that although nearly half of the men were past retirement age (65), three in every four were doing full-time work at the age of 66, while one in two were still working full-time at the age of 69. Financial need was given as the reason for remaining at work in 78.5% of all cases. Among the men above retirement age in social classes I and II (professional and related occupations) the incidence of unfitness was one in ten whereas in classes IV and V (semi-skilled and unskilled labour) unfitness rose to one in five.

Relating their findings to the complex question of retirement policy the authors concluded that, "If an advancement of retirement age were considered advisable for other reasons, there appear to be no medical grounds which would prohibit it."

Careful studies such as this are necessary and desirable both for the advancement of medical knowledge and for progress in social welfare. Since the emergence of the Welfare State in Britain such studies have increased in number and have been encouraged and facilitated by staffs of workers in the field of social medicine, not the least of whom are the biostatisticians. Departments of public health and welfare need information of this sort in formulating their policy. Yet it behooves us to remember that good intentions are not enough, and that caution must be exercised in presenting such findings to the policy-makers. To quote Sir Geoffrey Vickers,[2] "Our society is run by people who are accustomed and professionally trained to see and answer technological questions and financial questions, legal questions and administrative questions. Very few people are accustomed and professionally trained to see and answer human questions about people as people." It does not require much imagination to see what would happen to such a report were its findings to appear in newspaper headlines or if politicians and pressure groups were to use it for their own purposes.

The fact that general practitioners co-operated in this study is good news. Research panels are part of the College of General Practitioners in Britain, and their value lies not only in promotion of research itself, but also in the stimulating effect it has on the participating general practitioner. It shows him that he too can make a contribution to medical research, and removes the barriers between him and the full-time scientist. The added interest in his own daily work will be of benefit to his patients as well as to himself.

W. GROBIN

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Medical News in brief

STATISTICAL STUDY OF THUMB-SUCKING

Two Chicago pædiatricians (*J. Pediat.*, 52: 566, 1958) made a statistical study of 2650 infants and children with reference to the habit of sucking the finger or thumb. They agree with others that the problem of thumb-sucking has been over-emphasized and has led to undue alarm in parents. In the present series 45% of the subjects sucked their thumbs; there was no sex difference. Breast feeding was not a significant factor in the incidence of thumb-sucking, nor did there appear to be any correlation between psychological problems and thumb-sucking. The average age at which the habit stopped spontaneously was 3.8 years, i.e. much beyond the two-year limit mentioned in the literature. It is doubtful whether the habit was associated in the present series with dental malocclusion. The authors thought that babies who took longer to feed tended to suck their thumbs. There was no correlation between colic and thumb-sucking. The habit terminated spontaneously in the great majority of patients, and at an early enough age to contraindicate the use of a dental device to stop the habit.

CHLORPROMAZINE IN TETANUS

Chlorpromazine has been reported as of therapeutic value on the muscle spasm of local tetanus in the rabbit. Two independent reports in *Lancet* (1: 987 and 991, May 10, 1958) discuss its use in human tetanus. The first report by Laurence and his associates in South Africa was of a controlled trial, in which chlorpromazine was compared with barbiturates. In a series of 75 tetanus patients given one or other drug at random there was no statistically significant difference in the outcome of the disease. Chlorpromazine was found easier to manage than barbiturates, because it controlled the convulsions without causing loss of consciousness or clinically noticeable respiratory depression. In the second report from Dundee, Scotland, Barr reports an unusual case of tetanus in a girl of 11, in which muscle spasm was limited to the jaw and one leg. Full sedative doses of phenobarbitone did not relieve the spasm but chlorpromazine did. Doses of 20 mg. by slow intravenous injections reduced trismus for five or six hours. A combination of phenobarbitone and chlorpromazine might be superior to chlorpromazine alone.

TREATMENT OF DERMATITIS HERPETIFORMIS WITH SULFAMETHOXYPYRIDAZINE

Dermatitis herpetiformis has been treated with sulfonamides for a number of years. Perry and Winkelmann of the Mayo Clinic (*Proc. Staff Meet. Mayo Clin.*, 33: 164, 1958) report their studies of the use of a new sulfonamide, sulfamethoxypyridazine (Kynex), whose special characteristic is the prolonged plasma concentration due to its slow excretion. Seven patients with dermatitis herpetiformis were treated with the new sulfonamide, their selection being based on the fact that other treatment had not controlled the eruption except in one case. They had all been given sulfapyridine in the past. Treatment began with 500 mg. of the drug four times daily for a few days, the dose being decreased as soon as the eruption was controlled; one tablet (500 mg.) a day was sufficient for good control in most instances. Blistering was suppressed and the patient was free from itching and burning. In this preliminary report, the authors point out that only observation over a prolonged period will determine whether the incidence of adverse reactions will prohibit the therapeutic use of the drug. Initial studies certainly indicate that it is effective.

CHLORPROMAZINE AND INSULIN COMA IN PSYCHOSES

In a New York State mental hospital, Fink and his associates (*J. A. M. A.*, 166: 1846, 1958) made a comparative study of the effects of intensive chlorpromazine therapy and of insulin coma in an open-ward, voluntarily hospitalized series of patients. Over a period of three months, patients selected at random received either the standard total of 50 insulin comas given five times a week, or intensive dosage of chlorpromazine with doses adjusted so as to fall just short of toxicity in each case. The latter meant a maintenance dosage varying from 300 mg. to 2000 mg. daily with a median of 800 mg. Though the course followed by patients in the two groups differed in many details, the end result at the time of discharge was essentially the same. Chlorpromazine was just as effective in modifying psychotic behaviour as was insulin coma. There was no difference as regards improvement rating on discharge, incidence of complications, or effects on the psychotherapeutic relationship.

Chlorpromazine had the advantages of being safer, easier to administer and more suitable for long-term management. Neither therapy altered the basic schizophrenic process.

DIFFERENTIAL TOXICITY OF AMMONIUM SALTS

The relationship between clinical hepatic coma and ammonium intoxication has been extensively studied in animals and humans. It has been assumed so far that toxicity of different ammonium compounds was approximately the same. Warren (*J. Clin. Invest.*, 37: 497, 1958) shows that this is not so. He determined the intravenous LD50 of several ammonium salts in mice and found that toxicity of the chloride, acetate, bicarbonate, carbonate and hydroxide increased in relation to their effect in raising blood pH. The toxicity of ammonium citrate appeared to be related more to the citrate element than to the ammonium.

It has been shown that most patients in hepatic coma develop a respiratory alkalosis due to hyperventilation with a blood pH as high as 7.7. This alkalosis may significantly affect toxicity of ammonia in the blood and may partly account for the poor correlation between blood ammonia levels and hepatic coma. Administration of acidifying agents or carbon dioxide to patients in hepatic coma might be beneficial.

(Continued on advertising page 38)

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REVIEW ARTICLE

CORONARY VASCULAR ANASTOMOSES BY INTERNAL MAMMARY ARTERY IMPLANTATION*

ARTHUR VINEBERG, M.D., C.M., *Montreal*

TODAY coronary atherosclerosis which results in coronary artery heart disease is a most controversial subject in regard to etiology, prognosis and, in particular, treatment. However, there seems to be full agreement that narrowed or blocked coronary arteries may produce myocardial ischæmia. There is further agreement that anginal pain is a reflection of the inability of myocardial fibres to obtain sufficient oxygenated blood to meet energy demands. The end result of this complex biochemical problem is a mechanical obstruction to the free flow of oxygenated blood into the myocardium.

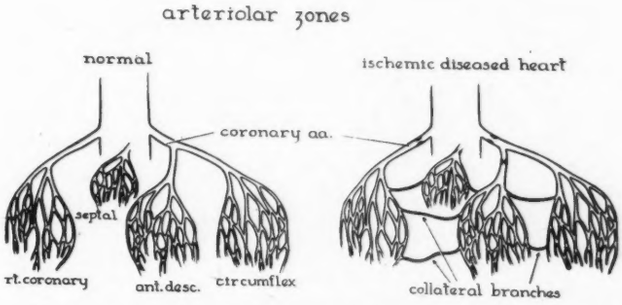

Fig. 1.—Main coronary arteries branch to join separate arteriolar networks lying within the myocardium. In 10% of normal hearts these arteriolar zones are joined by interzonal arterioles. In diseased hearts these collateral arterioles are almost always present (98%). In the normal or diseased heart, vessels larger than capillaries have not been demonstrated entering the heart from extra-coronary sources.

Our present concept of the myocardial circulation in health and disease has been based upon certain anatomical and pathological facts, a few of which have either not been recognized or have been ignored by other workers. The first concerns the extensive arteriolar network lying within the myocardium and receiving arterial blood directly from the major coronary arteries. This network is divided into separate arteriolar zones supplied by a branch of a major coronary artery. Normally there is no communication between these zones, but the presence of ischæmias stimulates the formation of interzonal arterioles or collaterals (Fig. 1). These collateral arteriolar vessels join arteriolar zones, thereby distributing blood more freely throughout the heart muscle. Unfortunately these intracoronary anastomotic channels cannot bring fresh extracardiac arterial blood into the network. Proof of arteriolar connections between extracoronary blood sources and the myocardial network is lacking. From the myocardial arteriolar network (Fig. 2) arterioles communicate with (a) other myocardial arteriolar zones—collateral vessels; (b) lumina of ventricles—arterioluminal vessels; (c) myocardial sinusoids lying between myocardial fibre bundles—arteriosinusoidal vessels; (d) capillary network lying about each myocardial fibre, and (e) the venous system.

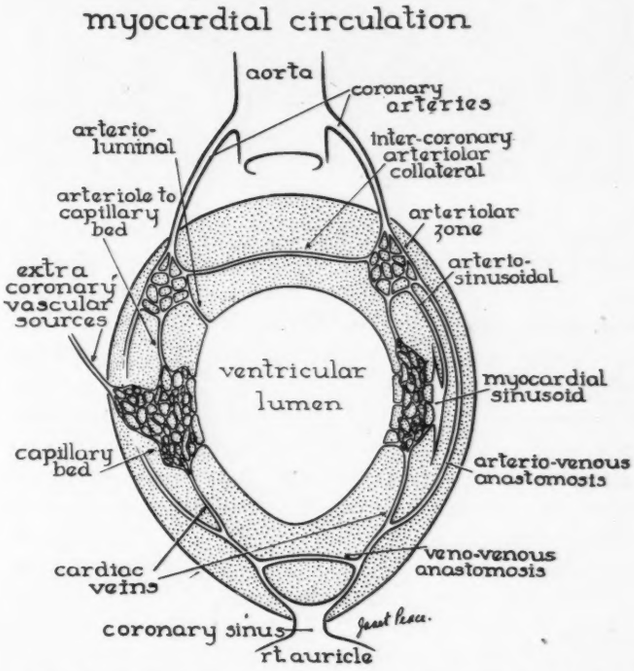

Fig. 2.—Schematic representation of normal myocardial circulation. Zoned myocardial arteriolar networks are supplied by main coronary arteries. From these arteriolar plexuses, arteriole-sized vessels leave to communicate with (a) other myocardial arteriolar zones, (b) lumina of ventricles—arterioluminal vessels, (c) myocardial sinusoids lying between myocardia, (d) capillary bed about muscle fibres, (e) venous system—arteriovenous fistula.

Coronary artery atherosclerosis generally invades the major vessels in their epicardial course. The myocardial arteriolar network is usually free of disease. When a coronary artery becomes narrowed, the volume of blood entering its arteriolar zone is diminished, thus decreasing the amount of oxygenated blood available for distribution throughout the network. This localized lowered oxygen tension stimulates the formation of collateral arterioles. These rapidly develop and, provided the neighbouring coronary arteries are healthy, they carry blood from the non-ischæmic to the ischæmic zone. However, when disease has affected the supply coronary arteries of the neighbouring arteriolar zones, there is insufficient oxygenated blood to spill over into the severely ischæmic zone. Once this situation has developed, vasodilators may relieve anginal pain but do not increase the myocardial blood supply. Theoretically, this can only be improved naturally by (1) the opening of arterioluminal vessels, (2) the en-

*Presented at the Annual Meeting of the International College of Angiology, 1957. From the Department of Experimental Surgery, McGill University; the Department of Cardiac Surgery, Royal Victoria Hospital; and the Institute of Cardiology, Montreal, Canada. This work has been made possible through grants generously given by the Department of National Health and Welfare, Ottawa, Canada.

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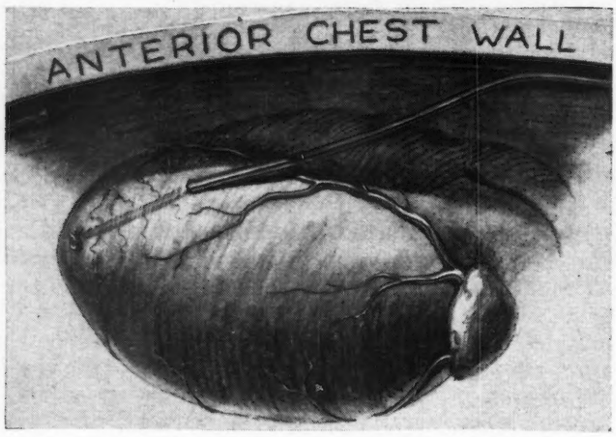

Fig. 3.—Drawing showing internal mammary artery detached from chest wall and buried in myocardial tunnel made in left ventricle.

largement of thebesian canals, (3) the development of arteriole-sized communications between the myocardial arteriolar network and an extracoronary blood source. There is little anatomical evidence in normal or diseased hearts to show that any one of these three sources is ever tapped. The chance of myocardial survival with all main coronary vessels blocked is very slim indeed. The occasional case of this type previously reported must be re-examined in the light of more recent mass injection studies by Schlesinger. Perhaps a conus branch or other aberrant coronary vessel was responsible for myocardial survival in the reported cases.

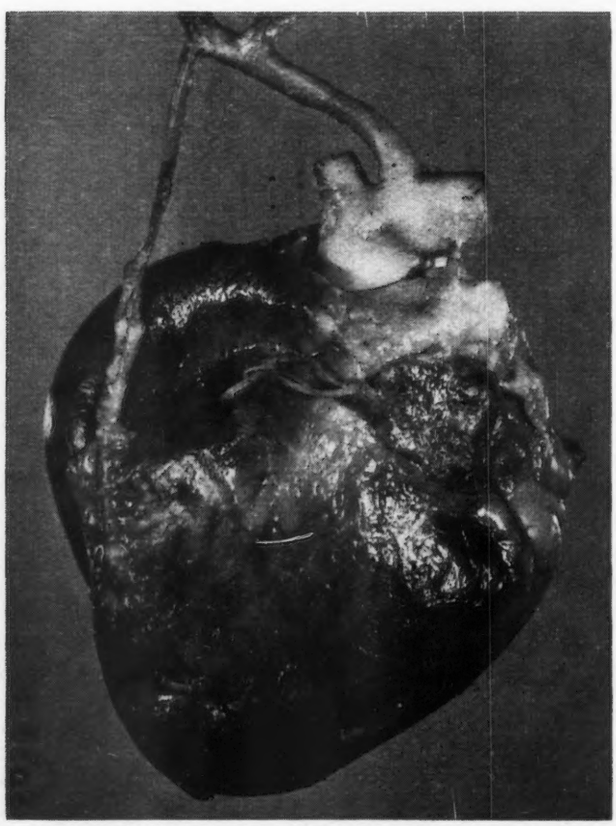

Fig. 4.—Dissected left subclavian artery and internal mammary artery, showing internal mammary artery in left ventricle seven months after implantation.

There is much confused thinking at present with regard to anastomoses between the coronary circulation and the extracoronary blood supply. Unquestionably, anastomoses exist at the points of pericardial reflection over the great vessels as they enter and leave the heart. Unfortunately, these much described anastomoses are capillary in size, are superficial, and are mostly with the vessels of the atria. There is no evidence at present to show that these existing capillary anastomoses enlarge in response to myocardial ischæmia or following bilateral internal mammary artery ligation.

If the above concept of the coronary circulation in health and disease is correct, surgical procedures

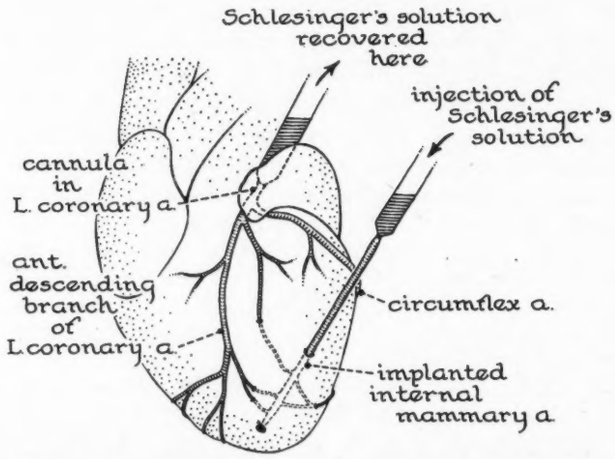

Fig. 5.—Drawing to show Schlesinger mass injected into implanted internal mammary artery, filling arterioles of left ventricle and coming out of cannula placed in left coronary artery.

are needed to relieve the myocardial ischæmia caused by the blocking of the main coronary arteries by atherosclerosis.

There are various possible surgical approaches to the problem:

1. To resect the diseased coronary artery and either anastomose a systemic artery to its distal end or insert a homograft. Experimentally at least 50% of these grafts block, which is the experience with replacement grafts in small vessels in the human extremities.

2. To scrape out the obstruction by endarterectomy. This may be of value in some cases but, again, following the experience of endarterectomy in other areas, it may prove not too successful.

3. To obtain wider distribution of blood by coronary sinus ligation (Beck I). Very little extracoronary oxygenated blood is delivered after this operation.

4. To perform a by-pass operation, in which the points of coronary artery obstruction are by-passed by:

(a) application of surface grafts which form superficial coronary vascular anastomoses, or

(b) vascular myocardial implants which, theoretically, are capable of pouring fresh oxygenated blood into the entire myocardial arteriolar system.

The vascular implant operative procedures are designed to pour extracardiac blood into the ventricular arteriolar network at points distal to the areas of coronary artery disease.

Twelve years ago the left internal mammary artery was detached from the chest wall and buried within a tunnel in the left ventricle of an animal's heart (Figs. 3 and 4).

To the astonishment of all, the buried artery not only remained open, but formed a connection between itself and the coronary circulation (Fig. 5). During the ensuing years well over 1500 animal experiments have been performed in order to determine why an artery, tied and cut at its

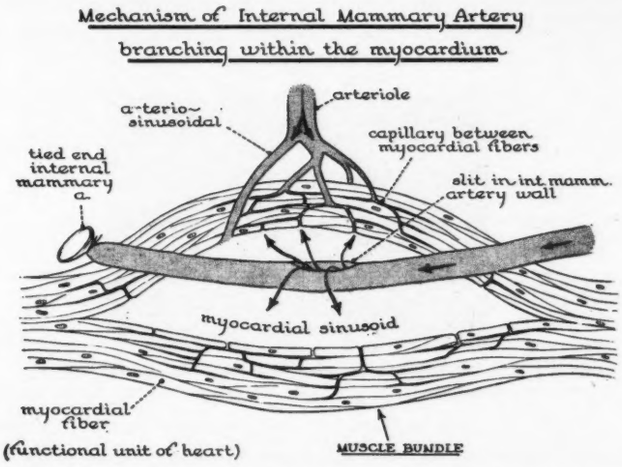

Fig. 6.—Drawing of implanted internal mammary artery in left ventricle with opening in side of vessel. Blood escapes from internal mammary artery into myocardial sinusoids, which is why the implanted vessel remains open until its own branches join the coronary arterioles.

distal end, and buried in a new environment, such as the myocardium, remains open for years. Our investigations showed that the artery remains open if it is allowed to bleed from an open side branch into the myocardial tunnel where the escaped blood is taken away through the medium of the myocardial sinusoids (Fig. 6). After 12 days the implanted internal mammary artery starts to bud

TABLE I.—ORGAN VASCULARIZATION BY ARTERY OR PROSTHESIS IMPLANTATION

Author	*Artery or prosthesis*	*Organ*
Experimental:		
Vineberg, Montreal	(a) Internal mammary artery	Left ventricle
	(b) Double aortico-homograft	Left ventricle
	(c) Polyethylene thebesian canal	Left ventricle
Glenn, New York	Internal mammary artery	Left ventricle
Liebow, New Haven	Splenic artery	Left ventricle
Blalock, Baltimore	(a) Internal carotid	Left ventricle
	(b) Aortico-homograft	Left ventricle
Wilson, Bristol, England	Internal mammary artery	Left ventricle
Davis, Miami, Florida	Splenic artery	Kidney and liver
Smith, Bradington, Florida	(a) Aortico-homograft	Left ventricle
	(b) Aortico nylon tube	Left ventricle
Massimo, Florence, Italy	Polyethylene thebesian canal	Left ventricle
Human coronary artery disease:		
57 cases, Vineberg, Montreal	Internal mammary artery	Left ventricle
35 cases, Walker, Charleston	Internal mammary artery	Left ventricle

Fig. 7.—Digestion cast of animal heart made to show implanted internal mammary artery lying in myocardium. Part of cast has been cut away, revealing early branching of internal mammary artery 12 days after implantation.

true arterioles (Fig. 7). These arterioles within a few weeks join directly with the arterioles of the ventricular myocardium, thus forming mammary-coronary anastomoses through which extracardiac arterial blood is delivered to the myocardium, and which are still present many months to years later (Fig. 8).

It has been found that the frequency and duration of mammary-coronary anastomosis is dependent upon:

1. The technique of internal mammary artery preparation and implanatation, and

Fig. 8.—Digestion cast of animal heart made by injecting implanted internal mammary artery with vinyl plastic seven months after implantation. Part of cast cut away to show size of branches which have grown from implanted internal mammary artery and have joined with surrounding coronary arterioles.

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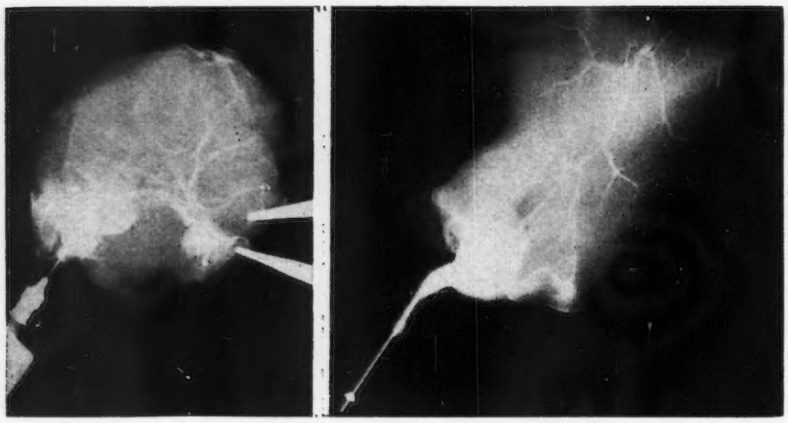


Fig. 9.—(a) Roentgenogram showing splenic artery implanted into kidney. Outline of kidney circulation made by injecting implanted splenic artery with radiopaque medium. (b) Roentgenogram showing splenic artery implanted into liver. Outline of liver circulation made by injecting radiopaque media through implanted internal mammary artery. (Photograph by courtesy of Davis.)

2. The character of the myocardium into which the implant is placed.[1-10]

The idea that an internal mammary artery could be detached from the chest wall and left in a myocardial tunnel without immediate or delayed thrombosis has been for a long time rejected. However, that fact has been confirmed by many workers (Table I), and the principles upon which it is based utilized for other vessels in the heart, kidney and liver. Kline[11] reports that the splenic, and Blalock[12] the carotid artery, remains open after implant into the ventricle. Smith has found that aortico-homografts as well as aortico nylon tube grafts remain open and form anastomoses. In our hands this has occurred but the percentage of thrombosed grafts was extremely high. Davis[14] (Fig. 9) has found that vascular anastomoses develop between an implanted splenic artery and the vessels of the kidney and liver after implantation.

In 1950, in our laboratory, an attempt was made to create artificial thebesian canals by placing an open polyethylene tube or homograft in the left ventricular lumen and burying the other end in the myocardium.

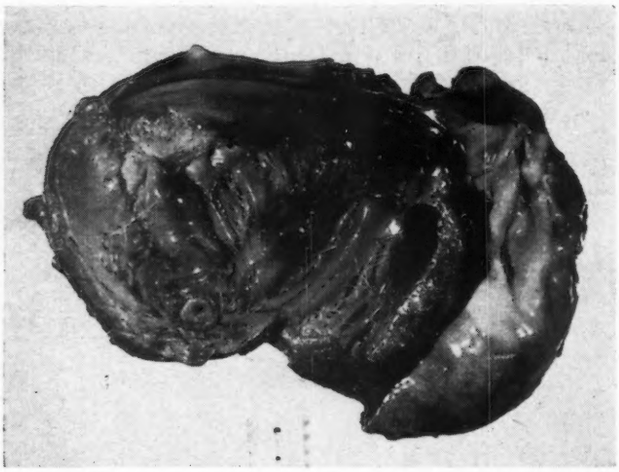


Fig. 10.—Artificial thebesian canal made by inserting polyethylene tube into left ventricular lumen and burying other end in myocardium. Note patent lumen. (Reported by author in this Journal 1953.)

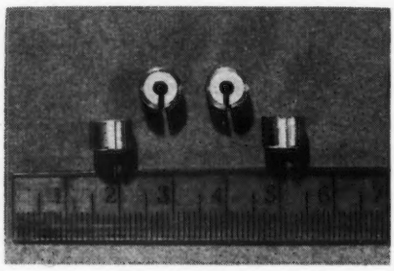


Fig. 12.—Photograph of ameroid constrictors used to constrict slowly coronary arteries at their origins in animals. Note ameroid casein plastic with slot to fit over artery and encased in steel jacket. The casein plastic absorbs water, swells, and constricts coronary artery. Rate of water absorption controlled by coating ameroid surface with Vaseline.

Some of these remained open (Fig. 10) but seldom showed vascular communications with the ventricular arteriolar network, and therefore the procedure was abandoned.

More recently, using the principles upon which internal mammary artery implantation has been based, Massimo[16] has succeeded in obtaining a vascular anastomosis between the left ventricular

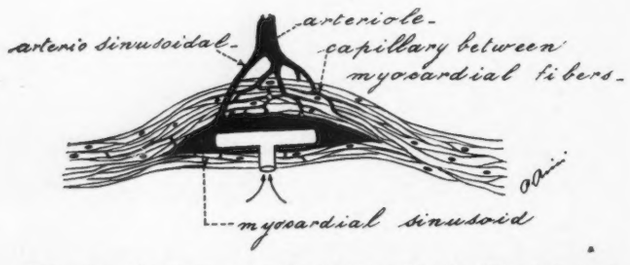


Fig. 11.—Drawing of polyethylene T-tube lying in myocardium and connecting with left ventricular lumen. (Courtesy of Massimo, *J. Thoracic Surg.*)

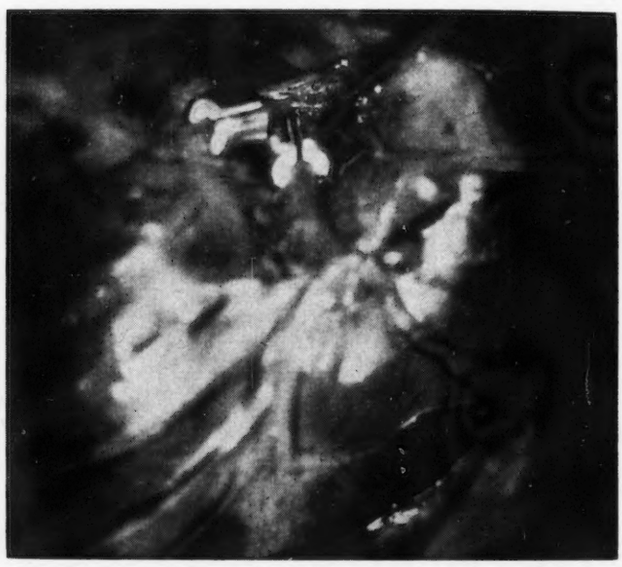
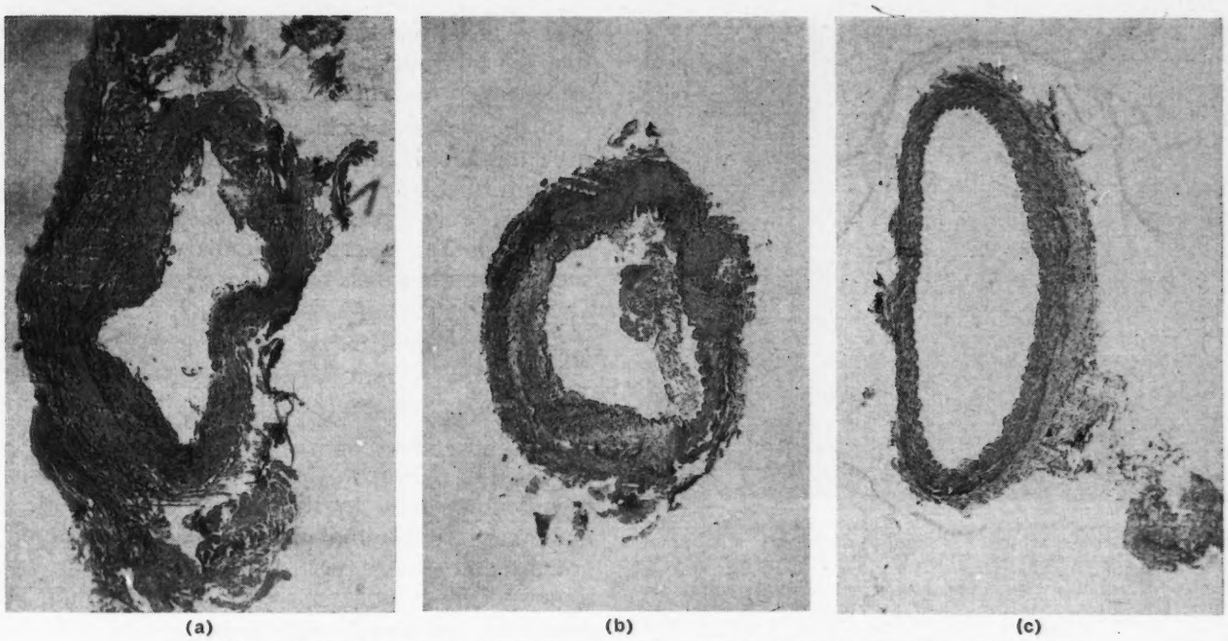


Fig 13.—Photograph to show ameroid constrictors on anterior descending and circumflex arteries.



(a) (b) (c)

Fig. 14.—Photomicrograph of sections through anterior descending artery (a) proximal, (b) through, (c) distal to site of ameroid constriction. Note narrowing of coronary artery proximal to and at site of ameroid constrictor compared with normal artery lumen just distal to point of arterial constriction.

cavity and the arteriolar sinusoidal myocardial meshwork (Fig. 11).

Now, there is little doubt that an implanted internal mammary artery sends out branches which join with the arteriolar ventricular network. The experimental proof of the value of this vessel and the frequency of mammary-coronary anastomosis has awaited a satisfactory method of producing chronic coronary artery occlusion which, fortunately, was developed in our laboratory two years ago by Litwack.

An ameroid tube encased in a steel jacket is placed around the origins of the anterior descending and circumflex coronary arteries (Figs. 12 and 13). The ameroid material absorbs water, expands, and slowly constricts the two coronary vessels. The rate of water absorption may be varied by coating the ameroid with various substances. A coating of Vaseline (petrolatum) prolongs the time taken for the ameroid to absorb water, swell, and constrict the coronary vessels. The thickness of the Vaseline coat varies according to the length of time the ameroids are left in the Vaseline bath and the temperature of the bath. Ameroids covered with a thin coating of Vaseline and placed around the anterior descending and circumflex branches of the left coronary artery caused death of all control animals within 28 days, whereas those more heavily coated took an average of 14 weeks to kill the control animals. In a recent series of control animals, ameroid constrictors were placed upon the anterior descending and circumflex arteries by Deschene, and all controls were dead within 14 weeks. Death usually occurred suddenly during exercise or excitement while at the animal farm. Four of the animals of this series, brought back to the laboratory, dropped dead after being deliberately excited; in each instance, when the thorax was opened, there was ventricular fibrillation. The degree of arterial constriction amounted to a reduction of internal diameter varying between one-half and one-third of normal (Fig. 14).

In a series of 20 internal mammary artery implantations carried out at the same time as the placing of ameroid constrictors (Table II), the animals which were exercised or excited by dog

TABLE II.—VALUE OF INTERNAL MAMMARY ARTERY IMPLANTATION IN PROTECTING THE VENTRICULAR MYOCARDIUM MADE ISCHÆMIC BY CORONARY AMEROID CONSTRICTORS

Time after internal mammary artery implantation + ameroid coronary constrictors	*Number of animals*	*Extent and frequency of mammary-coronary anastomoses*	*Cause of death*			
			Exercise and excitement			
			Natural	*Induced Moderate*	*Induced Severe*	*Sacrificed*
2 to 4 weeks	5	Anterior ventricular wall..... 3 of 5	5	—	—	—
5 to 12 weeks	8	Anterolateral ventricular wall.... 8 of 8	8	—	—	—
20 to 30 weeks	6	Entire left ventricle..... 6 of 6	0	0	0	5
			(Unable to kill by exercise)			

Total open internal mammary artery implants—17 of 19=89%
Mammary-coronary anastomoses—16 of 19=84%

NOTE: Of 20 controls 17 died within 29 weeks naturally (average 14 weeks)
3 died following induced moderate exercise.

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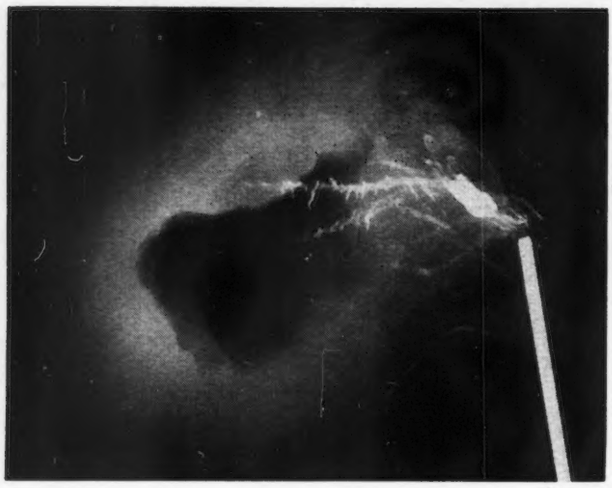

Fig. 15.—Roentgenogram of left ventricle injected with Schlesinger mass through implanted internal mammary artery less than five weeks after implantation. Animal died because of myocardial ischæmia caused by constriction of anterior descending and circumflex arteries by ameroid constrictors. Note: At this stage internal mammary artery communicated with arterioles of the anterior ventricular wall only.

fights less than five months after implantation died, and yet there were patent internal mammary arteries with mammary-coronary anastomoses. However, injection of these internal mammary arteries with Schlesinger's mass showed that under five weeks the internal mammary artery anastomosed only with the arterioles of the anterior ventricular wall (Fig. 15). Between five and 12 weeks they extended to include the antero-lateral left ventricular arterioles, and the injection mass did not reach the posterior left ventricle wall. There were six animals which lived beyond five months and could not be killed by hard exercise. One died later from distemper. Five were sacrificed and in every instance the Schlesinger mass injected through the internal mammary artery had filled the arterioles of the entire left ventricle (Fig. 16).

In the series of ischæmic animal hearts, 89% of the implanted internal mammary arteries were patent and 84% formed mammary-coronary anastomoses. There was minimal to no intimal proliferation in the internal mammary arteries left in such ischæmic myocardia.

SELECTION OF HUMAN PATIENTS WITH CORONARY ARTERY HEART DISEASE FOR REMEDIAL SURGERY

In treatment of human coronary artery disease, *selection of the type of patient* for remedial surgery is very important. In 1950, when the first internal mammary artery implant was performed upon a human case, there was no opportunity to select patients. The only patients reporting to the Montreal group for surgery were desperate, disabled, and pain-ridden people—a large percentage of whom were bed-chair invalids. Experience quickly showed that the proper selection of patients for coronary heart disease surgery should be largely dependent upon the stage of development of their disease, and the following criteria were agreed upon:

1. Proven coronary artery disease, with typical angina pectoris pain. The presence of coronary artery disease in itself is not sufficient for surgery, unless the patient suffers anginal pain which is truly causing difficulty.

2. At least one to two years of adequate medical treatment.

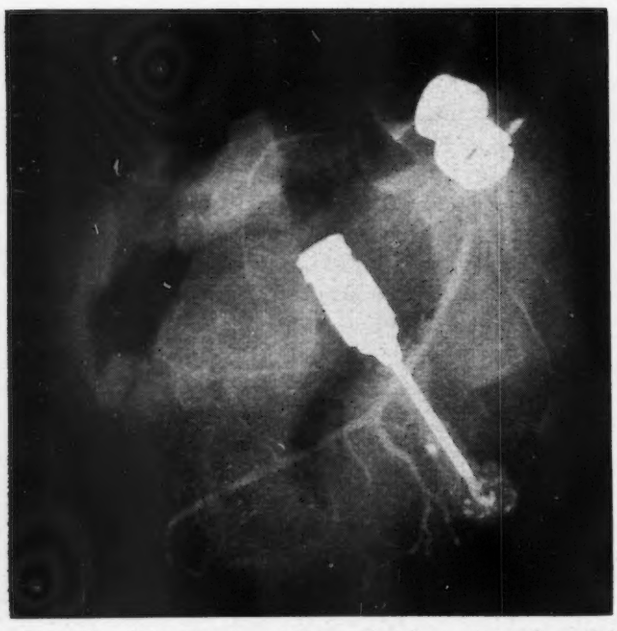

Fig. 16 (a).—Roentgenogram showing circumferential filling of left ventricle by Schlesinger mass injected through internal mammary artery implanted more than five months previously. Note: This animal could not be killed by severe exercise, even though anterior descending and circumflex arteries were markedly narrowed at their origins by ameroid constrictors.

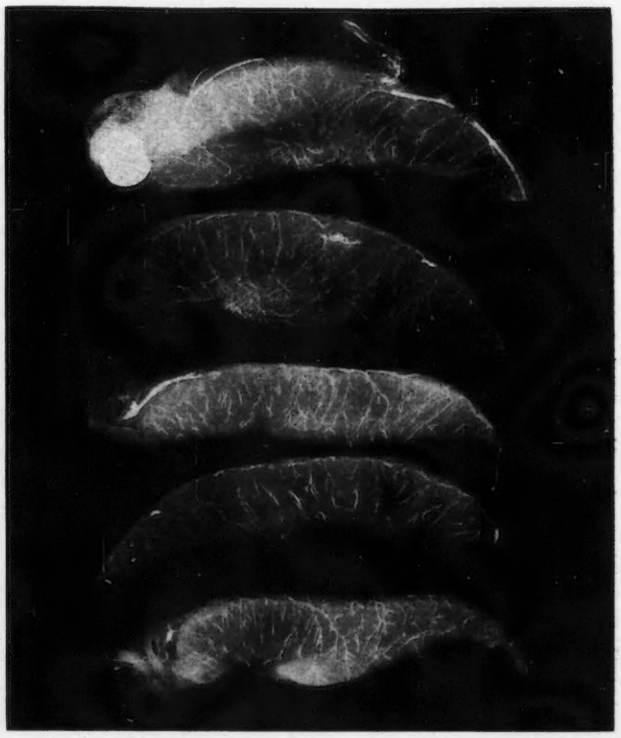

Fig. 16 (b).—Same heart sectioned to show full thickness of left ventricular wall.

CONTRAINDICATIONS

There are certain contraindications to internal mammary artery implantation; for example, surgery should NOT be performed

(a) When the patient is asymptomatic.
(b) When there is evidence of disease activity.
(c) When there is evidence of left ventricular failure.
(d) When other incurable disease co-exists.
(e) When the patient has angina decubitus.

EVALUATION OF RESULTS

Evaluation of the treatment of coronary artery disease is difficult because of the numerous and unpredictable variations which occur during the natural course of the disease, and because at the present time there is no objective laboratory method of measuring improvement in myocardial circulation. At present, the observer must rely upon the following criteria as evidence of improved myocardial circulation, namely:

(a) Survival.
(b) Disappearance of anginal pain for more than six months.
(c) Increase in work and exercise tolerance.
(d) Improvement in electrocardiogram.
(e) Failure to develop fresh infarction.

In our experience there are two main groups of patients in whom entirely different results may be expected from revascularization surgery. These are:

1. Cases with angina at rest, without exciting cause (angina decubitus).

2. Cases with no angina at rest, without exciting cause. In previous publications the first group have been referred to as cases of "angina decubitus". This term, which refers to the onset of anginal pain when the patient assumes the decubitus position, has led to much misunderstanding and does not satisfactorily describe this group of patients. In this group, patients while at rest experience anginal pain for which there is no obvious exciting cause, such as talking, telephoning, watching television, or emotion. The coronary artery circulation is so reduced that the basic myocardial muscle energy demand necessary to maintain life at rest cannot be completely met, and myocardial ischæmia and anginal pain develop while at complete rest. Such hearts are beyond help since too much of the myocardium has been destroyed.

In the second group of patients, with no angina at rest without exciting cause, the situation is different. Many of the patients in this group have pain at rest but always associated with an exciting cause, such as eating. Many are awakened by pain during sleep, under which circumstances the exciting cause appears to be a drop in blood pressure or a disturbing dream. All patients in this group were able to walk at least 50 feet without pain and most were disabled and unable to work. Pain at rest, when it occurred, could always be related to some exciting cause.

OPERATIVE MORTALITY

The mortality for any operative procedure depends upon: (i) the method of estimating operative mortality, and (ii) the selection of patients.

In this series of patients, any death of a person within 28 days of operation, in or out of hospital, is listed as an operative mortality. In coronary artery heart disease, postoperative deaths are mostly due to a fresh coronary artery thrombosis. This may occur during operation, immediately after operation or, as in one of our patients, three weeks after operation. It is quite true that the patient died of his disease, but it was still an operative death and cannot be excluded from operative mortality statistics as has been suggested by Glover.[18] Dana and Ohler[19] have found that the mortality of patients suffering from angina pectoris at the time of undergoing general surgery is 7.8%.

With regard to case selection, it is obvious that the operative mortality rate should scale down from the far advanced cases to those which are asymptomatic.

In our series of 59 patients the cases have been divided into those with angina at rest without exciting cause—17 cases, with an operative mortality of 59%, and those with no angina at rest without exciting cause—40 cases, operative mortality 5% (Table III).

TABLE III.—INTERNAL MAMMARY ARTERY IMPLANTATION
OPERATIVE MORTALITY WITHIN 30 DAYS OF OPERATION

	Cases		
Angina at rest without exciting cause	17	10 deaths	59%
No angina at rest without exciting cause	40	2 deaths	5%
Total number of cases	57		

TABLE IV.—INTERNAL MAMMARY ARTERY IMPLANTATION
LATE MORTALITY
4 MONTHS TO 6 YEARS AFTER OPERATION

Angina at rest without exciting cause:	
Total number of cases	17
Survived operation	7
3 died 12 months to 4 years after operation:	
(i) Cancer of pancreas.	
(ii) Aplastic anæmia.	
(iii) Heart.	
(*2 patients pain-free and working.*)	
No angina at rest without exciting cause:	
Total number of cases	40
Survived operation	38
8 died 4 months to 6 years after operation:	
(i) Rupture right ventricular aneurysm.	
(ii) Dissecting aortic aneurysm.	
(iii) Died pushing car out of snow—rupture ventricular scar.	
(iv) Died after riding horseback.	
(v and vi) Right ventricular infarction.	
(vii and viii) Known cardiac deaths.	
(*5 patients had no pain or slight pain and were working at time of death*).	

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TABLE V.—RESULTS OF INTERNAL MAMMARY ARTERY IMPLANTATION IN ANGINA AT REST WITHOUT EXCITING CAUSE

TOTAL NUMBER OF CASES..... 17	OPERATIVE DEATHS..... 10 (57%)	LATE DEATHS..... 3 (18%)

Unable to work before operation..... 17 (100%)

Condition of 7 survivors	*6 months to 7 years after operation*	
No pain or slight pain	3 (43%)	86% of survivors improved. 35% of original group
Less pain	3 (43%)	
Same or worse	1	
Returned to work	4 (57% of survivors—24% of original group)	
No. original group still alive	4 (24%)	2 (3 years 9 months to 6 years 11 months) 2 (2 years 11 months)
Working full time	1 (6% of original group)	
No pain or slight pain	1 (6%)	
Less pain	1 (6%)	
Same or worse	1	

LATE MORTALITY

The cause in late deaths of patients of both groups is shown in Table IV. Three were non-cardiac deaths, and two were caused by right ventricular lesions.

POSTOPERATIVE RESULTS

An analysis of the patients with angina at rest without exciting cause reveals that, in addition to a high mortality rate in this group, only one patient is working full time, and only two patients or 12% of the original group may be considered to have improved after internal mammary artery implantation (Table V), whereas, for the 40 patients with no angina at rest without exciting cause, although 80% were unable to work before operation, 78% of the survivors and 70% of the original group were pain-free, or had slight pain or less pain, and *88% of the survivors returned to work.*

A recent survey made six months to seven years after operation reveals that 30 patients, or 75% of the original group, are still alive. Twenty-four, or 60%, are working full time—16 of these 3 years to 6 years 9 months after operation, and 8 of them 6 months to 2 years 9 months after operation. Twenty-five or 66% are still improved, being pain-free or having slight pain or less pain (Table VI).

During the past 15 years much criticism has been levelled at the internal mammary artery implant procedure. Perhaps the most serious of these criticisms has been the statement by others that the implanted arteries block, by thrombosis or intimal proliferation, when left in animal hearts for more than five months. However, the authors of these statements have found that, when our technique has been carefully repeated, the ischæmic hearts of animals are successfully revascularized just as we have shown early in this paper. Our statements based on animal experimentation have now received confirmation in pathological studies made on the implanted internal mammary arteries of 14 patients who died from six hours to four years after operation.

EARLY DEATHS

Of the 14 patients studied, 8 died within 21 days of operation. Seven of these had had a fresh coronary occlusion and the internal mammary artery was open. In two cases injection of the implant was done with India ink which entered the coronary vessels 82 hours to 21 days after operation.

LATE DEATHS

A study of the six patients who died four months to four years after operation showed that

TABLE VI.—RESULTS OF INTERNAL MAMMARY ARTERY IMPLANTATION IN NO ANGINA AT REST WITHOUT EXCITING CAUSE

TOTAL NUMBER OF CASES..... 40	OPERATIVE DEATHS..... 2 (5%)	LATE DEATHS..... 8 (20%)

Unable to work..... 32 (80%)

Condition of 38 survivors (95%)—6 months to 7 years after operation		
No pain or slight pain	27 (75%)	78% of survivors 70% of original group improved
Less pain	1 (3%)	
Same or worse	8 (22%)	
Returned to work	32 (88% of survivors) (82% of original group)	
Number of original group still alive	30 (75%)	
Working full time	24 (60%)	16—3 years to 6 years 9 months. 8—6 months to 2 years 9 months.
No pain or slight pain	24	25 (66%) still improved
Less pain	1	
Same or worse	5	

(2 cases less than 6 months after operation not included)

TABLE VII.—CONDITION OF HUMAN INTERNAL MAMMARY ARTERY
6 HOURS TO 4 YEARS AFTER IMPLANTATION

Operative deaths autopsied	*Number cases*	*Time after implantation*	*Cause of death*	*Open I.M. artery*
8	2	6 to 24 hours	(a) Fresh thrombus left coronary (b) Fresh thrombus circumflex	2
	2	60 to 24 hours	Fresh thrombus circumflex	2
	1	82 hours	Penicillin allergy	1
	1	4 days	Fresh thrombus right coronary	1
	1	10 days	Fresh thrombus right coronary	0
	1	21 days	Fresh thrombus right coronary	1
	8			7(88%)
Late deaths autopsied				
6	1	4 months	Right coronary artery occlusion	0
	2	18 months	(a) Dissecting aortic aneurysm	1
			(b) Cancer of the pancreas	1
	1	3 years	Rupture right ventricle	1
	1	3 years 5 months	Cardiac irregularity	1
	1	4 years	Aplastic anæmia	0
	6			4(67%)
Total cases..14				11 (78.5%)

the internal mammary artery was open in four of the six cases. In one patient, who died of a ruptured right ventricular aneurysm, the only artery open in the heart three years ofter operation was the implanted internal mammary artery placed there three years before. The implanted vessel had a 60 to 70% lumen, and there appeared to have been no progress of the disease in the left ventricle from the time of operation to the time of death (Table VII).

One of the most interesting cases is that of a 60-year-old man who, at the time of internal mammary artery implant, was completely crippled with severe angina, and who returned to an 8-hour night shift in an aircraft factory where he worked for 18 months, pain-free, until he died of cancer of the pancreas. His heart was returned to Montreal, where 850 serial sections were made of the implanted internal mammary artery. It was found that the implanted internal mammary artery was widely open, without intimal proliferation at the entrance to the tunnel (Fig. 17).

Another patient who showed marked clinical improvement following internal mammary artery implantation returned to work, and died 3 years 5 months after operation. The right and left coronary arteries were cannulated and the internal mammary artery was injected with barium mass under gravity pressure at the Ford Hospital in Detroit by Dr. Edward Priest, who reported that the injection mass entered the internal mammary artery, filling the arterioles of the entire left ventricle, and subsequently appeared in the cannula which was placed in the left coronary artery.

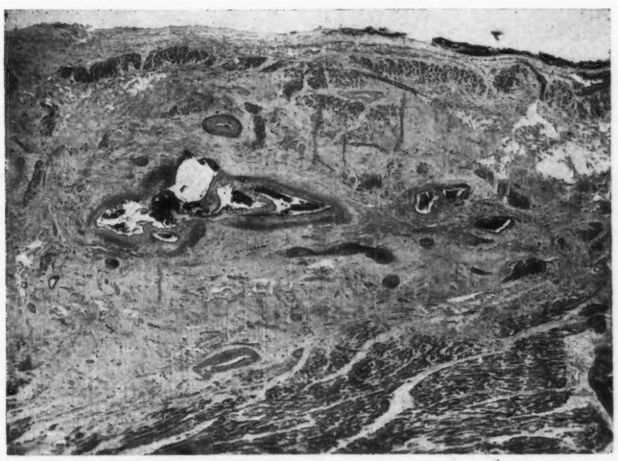

Fig. 17.—Photomicrograph of internal mammary artery one-third along the tunnel. Note active branching. This photomicrograph was made from the heart of a 60-year-old patient with angina at rest without exciting cause. Patient totally disabled before implantation; returned to eight-hour daily work, pain free; died of carcinoma of pancreas. The circumflex artery was injected antegrade with India ink and the injection mass was found in the internal mammary artery.

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GENERAL PRACTICE

EMOTIONAL DISORDERS IN LATER LIFE AND THEIR TREATMENT*

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VIRGIL SAID: "Age takes everything, even the mind away." Yet Virgil died 19 years before the birth of Christ. Then a newborn babe had a life expectancy of 20 years; a man of 70 was a rare specimen indeed. Thus 2000 years ago the followers of Hippocrates need have little concern about the emotional problems of the aged.

How different are things today! Almost 10% of the Canadian people are now over 65. On top of this there is much to suggest that emotional problems are more common in the aged. For instance, the suicide rate of old people (especially old men) is higher than the average for the population. Over 30% of the patients in provincial mental hospitals are past 65. Dr. Paul Hoch, Commissioner for Mental Health in the State of New York, suggests that for every old person certified to hospital as mentally ill, there are at least 10 more in the community equally sick and equally certifiable. Yet these are people who are never committed to state institutions. This is why the problem of emotional disorder in the aged is so important to the medical practitioner. He finds himself looking after many emotionally disturbed old people. There is nothing that he can do to avoid this situation, and he would be wise to study its implications. The purpose of this paper is to examine the problems arising from emotional disorders in later life, as seen in general practice. While not all of these questions can be answered, there is none the less much useful information about the old.

First let us briefly look at the role of emotion in illness. Is it easy for the doctor to know when a symptom is emotional in origin? Let me recount with chagrin a personal experience. About a year ago I was asked to admit a 68-year-old man to our Psychiatric Service. A surgeon had been investigating him for several weeks. Carcinoma was suspected but, as no tumour was found, he was referred to Psychiatry. The patient was definitely depressed. However, not only was he sallow and cachetic, but also he complained of severe abdominal pains. His appearance and his gastro-intestinal complaints made it hard for me to accept the absence of severe organic disorder. I delayed electrotherapy for several more days until more physical examinations had been completed. Finding nothing, we then treated his depression. Within a week after the electrical treatment began, he gained 5 lb. and three weeks later was discharged very much improved. Six months later, 30 lb. heavier, of ruddy complexion and exuberant in manner he returned to thank me for having given him "the right treatment". With some feelings of guilt I accepted his thanks. I consoled myself with the knowledge that it is not always easy to determine the significance of the emotional part of a symptom or to decide the best treatment when emotional and physical complaints are combined.

How do the patterns of emotional disorder in the aged differ from those occurring earlier in life? Generally speaking, there is no great difference. The imprint of age on the picture of emotional disturbance is not as clear as one would think. An aged person will often show signs of emotional illness as florid as those found in a 40-year-old. I have seen a man of 70 years in a state of manic excitement writing romantic poetry to a startled 20-year-old girl while his aged wife burned with ill-concealed anger. Dr. Osmond tells me that Goethe at the age of 80 did likewise.

As in the younger person, the most frequent way for the old to express emotional disturbance is through physical complaints. Their over-concern about constipation and the repetitive questions about minor details of sleeping and eating are often ways of saying: "Doctor, I am lonely and upset. Will you not comfort and reassure me?"

Now what are emotional disorders? Why do they appear? What part does emotion play in the operation of the human machine? Let us look at man as an organism trying to maintain his equilibrium. Just as he strives for acid base balance, optimum blood sugar levels, and blood pressure within normal limits, so he struggles for a state of emotional homœostasis. He does not feel comfortable when he is too sad, too mad, or even too glad. When something stressful happens to him, through his nervous and endocrine systems he tries to adjust himself to the new situation. Sometimes this adjustment cannot be made immediately. Then he becomes tense. *Then* he experiences emotion. These stirred-up feelings—joy, sorrow, and anger—which are called emotions affect the way he behaves. On the one hand they provide him with energy for greater effort. On the other, if long continued, they make him most anxious and unhappy. Then consciously or unconsciously he tries to do something about it.

The stresses which threaten our precarious balance are multitude. They include physical illnesses, for the real or fancied threats of sickness have always been a potent source of emotional trouble. They also include the scrambling of thought and feeling which occurs in mental illness. Finally there are the environmental and social threats that hang over man like the sword of Damocles.

There are many ways in which we can become emotionally disturbed. A brain damaged by prolonged vascular hypertension may lead to disturbed behaviour even in a person whose past life has run altogether smoothly. On the other hand a buried and forgotten childhood resentment may be suddenly brought to life by a chance experience. I remember a nice old lady who had lived a life of quiet calm. She became acutely disturbed and

*Presented at the Annual Meeting of the Canadian Medical Association, Edmonton, Alta., June 17-20, 1957.
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hostile when her sister, whom she had not seen for many years, died suddenly. It turned out that this event stirred up long forgotten yet unhappy memories. Finally the necessary dependency which often accompanies age may be a source of resentment, and this resentment combined with inevitable limitations in social activity frequently upsets the applecart.

The nature of the emotional symptoms may give no clues to the underlying troubles, any more than would an elevated temperature, or the onset of tachycardia, identify the disturbing physiological agent. However, the right questions will give some of the answers. Even if a careful history does not reveal much, it is always a necessary prelude to treatment. The oldster loves to be questioned about his early life—especially his childhood, for as one gets older the pleasant memories tend to linger while the sad ones drift away. Also, memory defects of organic origin are more marked for recent events. Hence, the memories of early experiences are sharper than those of more recent ones.

In diagnosing or treating psychiatric illnesses in those over 65, one runs into a mythology of misconceptions. First, that all mental disorders in this group are due to brain deterioration associated with senile change. Actually less than 50% of mental illness in the aged is due to known organic cause. Then there is the contradicting and equally inaccurate idea that senile changes with memory loss, confusion and disorientation are really not mental illnesses at all. Rather they are thought by some misinformed people to be isolated phenomena separate from the patient and his state of health, in the same way that some early philosophers separated the mind from the body. These senile symptoms are often dismissed with an airy: "He is not mentally sick, just confused, just old." Thus many people, including some psychiatrists, would deny that the mentally sick old man needs psychiatric consideration and care.

As it is important to clarify this confusion, let us define our terms of reference. We shall include in our discussion all types of mental illness of the aged, as seen by the family doctor in his office. There will be not only the grossly psychotic but also those with much milder memory loss and less confusion.

As in all classifications of mental disease, our grouping of emotional disorders of the old will be based on a combination of etiology and symptoms. The five groups listed are as follows:

1. Functional disorder (including schizophrenia and the affective psychoses).
2. Toxic disorders.
3. Cerebral arteriosclerosis.
4. Senile psychosis.
5. Psychoneurosis.

It must be pointed out that this is a sorting of convenience. These are in no way discrete syndromes—much overlapping exists.

1. Functional Disorder

The two great diagnostic categories usually included in the functional group are the schizophrenic and depressive illnesses. Though possible, it is unusual for a schizophrenic disorder to show itself for the first time after the age of 65. On the other hand, to have a first serious depression arise in an oldster is extremely common. The depressive picture is like that in the middle-aged. The patient looks dejected, shows little interest in his surroundings, and becomes slowed up in word and action. His appetite is poor; there is often great weight loss. He complains of waking early in the morning. His mood, which is very bad when he wakens, often improves during the day. The point of his depression is a feeling of guilt, of worthlessness, of uselessness, that he has done wrong—that he is bringing shame and disaster to his family. Questions to bring out such feelings include: "Do you really feel that life is worth living?" "Do you ever wish that you could go to sleep and never wake up?" Do not hesitate to ask direct questions about suicidal thoughts or attempts. Please consider such feelings seriously. Suicide in old people is much more common than is supposed—and almost always can be prevented by appropriate treatment.

The onset of depressive illness in the aged frequently follows surgery. It is common after prostatectomy or cataract removal, and as with my old gentleman the weight loss of the depression is often misdiagnosed as the cachexia of an undetected carcinoma.

There is one type of depression in which the depression itself is not easily detected. In this group the patient complains, like the old man described above, of somatic discomfort. A repetitive and sometimes unconvincing complaint of insomnia, fatigue, headache and other pain may be the mask of a real severe depression. Sometimes loss of libido is the most striking symptom.

Should one give electrotherapy when a diagnosis of depression has been made? If it is a mild one and the patient not too uncomfortable, one should usually wait. If the patient is suffering greatly or suicide is a danger, electrotherapy should be started as soon as possible. In expert hands, the procedure is astonishingly safe. The use of succinylcholine diminishes the danger of complications. When a patient is given intravenous thiopentone (Pentothal) before a treatment, fear and apprehension are usually avoided. Cardiovascular conditions require special attention; in the presence of cardiac failure, one avoids electrotherapy except under exceptional circumstances. Coronary thrombosis has been known to occur undetected between two electrical treatments. The consequence of treating a patient after such a recent infarct may be serious. However, often in a depression the risk of not giving electrotherapy to a patient is greater than the risk of giving it. Each case must be carefully considered.

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One word of caution here. As the depressed patient starts to improve, there is a brief period during which the suicidal risk is increased.

After electrotherapy the patient will temporarily develop confusion and memory loss. Both he and his family should be warned of this. They should be assured that except for the amnesia for the period immediately preceding treatment this memory loss will disappear.

You will notice that I use the word "electrotherapy" instead of electroshock or electroconvulsive therapy. Dr. Coburn introduced this change in nomenclature to our own department. We feel that it has helped counteract the apprehension that we believe the word "shock" has created.

The indiscriminate use of the so-called tranquillizers by some, is a worry to those who practise psychiatry. For depression, most tranquillizing agents are not only useless but even harmful, as they increase rather than lessen symptoms. The danger of creating a drug-induced depression should be considered when using rauwolfia or like agents while treating hypertension. Sometimes even as the blood pressure falls, the depression sets in.

2. Toxic Disorder

Just as it does to other organs, generalized toxæmia disturbs the function of the brain. Cardiac and renal disease are common causes of such mental change. The resulting psychotic symptoms, usually of sudden onset, are florid and fleeting. Recently I was asked to see an 83-year-old woman suffering from obstructive jaundice who had suddenly become noisy and disturbed. She had never been mentally ill before. She insisted that a large building was burning just outside her window. She described the firemen fighting the blaze and graphically told of people jumping to safety. She was especially disturbed because no one else could see the fire. She resented being contradicted and scolded for describing what she could see. The hallucinations and the emotional disturbance disappeared in two days as the jaundice subsided.

The emotional symptoms produced by toxic disorders are usually vacillating. The associated delusions are patchy and not organized. The chief therapeutic effort should be towards the cause of the toxic illness. Some psychiatrists suggest large doses of vitamin B to counter the toxin. Barbiturates should be used with the greatest caution as sometimes their unwise use is in itself the cause of toxic psychosis. Finally the ace in the doctor's deck is the skilled and sympathetic nursing care which the confused physically ill old person so urgently needs.

3. Cerebral Arteriosclerosis

Sclerosis of cerebral vessels often precipitates emotional disorder. The symptoms are like those of senile brain deterioration. How can these two be differentiated? The presence of generalized arteriosclerosis helps one decide. Usually the arteriosclerotic patient is the younger and his symptoms have more sudden onset. When a pleasant woman in her sixties with an unremarkable past history has an unexplained seizure followed by irritable confusion, then suspect cerebral vascular disease. The patient whose mental illness results from cerebral sclerosis creates special problems for the doctor. Supportive care and good supervision are immediately necessary. Yet both the patient and his relatives shrink from overcrowded, understaffed archaic institutions which we call provincial mental hospitals. However, the general hospitals usually refuse to admit such sick people. This attitude of the general hospitals should be questioned. During the acute phase most if not all of this group could be treated in a general hospital, provided that the hospital had some nursing staff with psychiatric training. Contrary to common belief, these patients can usually be rehabilitated to their homes—often within a few weeks. Here at least is a place where the family doctor can help combat society's disgraceful efforts to banish mentally sick people to large, cheap concentration areas far removed from the communities' hospitals.

This type of problem calls out the family doctor's greatest psychotherapeutic skill. Not only must he deal with the patient but also he must work and plan with the other members of the family. Tranquillizing drugs can be used safely and with good effect. Rauwolfia should be employed with caution because a lowering blood pressure may increase confusion in a brain adjusted to higher pressure levels. Chlorpromazine (Largactil) and related drugs may be used in dosage up to 150 mg. a day.

4. Senile Psychosis

The arteriosclerotic syndrome often shades imperceptibly into the symptoms of senility. The senile patient is usually older and the symptoms are less dramatic, less variable. The emotional disturbances are chiefly chronic irritability and expressed frustration. The accompanying confusion and disorientation are a most constant feature of the picture. Here again, the patience, tact and skill of the physician are challenged. The family at first will not recognize the increasing irritability as illness—to them it is bad temper and requires repayment in like coin. The emotional attitude of the patient's family is a mixture of anger towards the patient, guilt about its own attitude, irritation towards the physician because he "does nothing" and annoyance at the province for not providing better hospital facilities for the aged. In this emergency, time and patience are the physician's most important tools. He should go easy on the barbiturates but make fairly generous use of the tranquillizers. Electrotherapy usually has no place

unless depression is marked. Sometimes a period in general hospital will help to ease the shock of the journey to the province's inadequate resources for the aged mentally ill. Certainly these patients are entitled to thoughtful investigation and to some therapeutic regimen.

If admission to the provincial hospital is needed, it should be made clear that this is to be looked upon as a temporary step and that the patient will be eventually returning home. Too often, after the guilt and grief of seeing a patient go to provincial hospital has abated, the family gently but firmly close the door against his return. The physician should actively prepare the family to expect him back. Finally, just a word about sending an old person in an almost moribund state, on a 100 to 200 mile trip to a provincial hospital. If death is imminent, try to let this take place peacefully at home or in a local hospital rather than allow the situation to be aggravated by a long and difficult journey.

5. PSYCHONEUROSIS

The old, like the rest of us, are prone to neurotic symptoms. Usually these are tiresomely repeated somatic complaints in the absence of important organic disease. Sometimes they are equally unwarranted anxieties over family or future. Like all neurotic symptoms, those of the aged are consciously or unconsciously directed towards gain. One must remember that the symptom, be it "Doctor, I feel so frightened" or "I cannot stand this steady pain," has a message and a purpose. This is why simple reassurance that there is no organic trouble does not take the complaints away. Often the message is: "Doctor, I feel lonely, bored, and useless."

The trouble arises both from the patient's present and his past. He does feel insecure and neglected because, as the poet says: "Age with stealing steps hath clawed [him] with his clutch." Yet the stuff of his anxieties is borrowed from his past—childhood fears, adult disappointments. All this does *not* require intensive psychotherapy. Usually such should *not* be attempted. Rather there is needed some dignified attention from a respected physician—a doctor with a sense of humour who will not let the patient's fears induce anxieties in himself. Too often the doctor is disturbed by his need to do something definite, to see clear-cut therapeutic results. Too much medication, too much investigation, does harm rather than good. What the patient mostly needs is that very scarce commodity, some of the doctor's time.

Sedatives should be used with a restraint too seldom seen. Tranquillizers can be beneficial but should be in limited doses and for limited periods. Wise words (but not too many words) for the family together with quiet reassurance and interest for the patient will best fill the bill. Do not feel the need to remove the symptoms. After all, the patient *does* want to see his doctor. If his symptoms go entirely, then he has lost his key to your office.

SUMMARY

Emotional problems more than any other bring the old to the doctor's office. Less than half of these mental disturbances arise from cerebral organic change; the rest are the depressions, toxic confusions or the neurosis found at any age.

The outdated pessimism about emotional illness in the old is quite unwarranted. Most emotionally sick old people respond to treatment as do people of other age and other ill. Most of this treatment is and will be the responsibility of the family doctor. His efforts with the emotionally ill aged can bring him his greatest satisfaction.

The magic lies not in drugs—these may be necessary and useful—but in that doctor-patient relationship which is the essence of successful medical practice.

Our trend towards an older population will increase the time the doctor has to spend with the emotional disorders of the old. To a doctor who likes and enjoys helping people and who is interested in every act, even the last, of the human comedy, this increasing challenge should be accepted with pleasure.

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A COMPARISON OF THE CANADIAN COLLEGE AND THE AMERICAN ACADEMY OF GENERAL PRACTICE

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As PRESIDENT of the College, I was privileged to attend two Scientific Assemblies of the American Academy of General Practice: one at St. Louis, Missouri, last year, and more recently, the Tenth A.A.G.P. Scientific Convention held at Dallas, Texas, March 24-27, in co-operation with Dallas Southern Clinical Society. On both occasions I had the opportunity to bring greetings from our College of General Practice to the House of Delegates of the A.A.G.P.

There is a close parallel between the American scientific sessions and our own. As in all other comparisons between the two countries, the population factor of ten to one must be applied to appraise the absolute figures. The A.A.G.P. with its very large membership drew 3600 doctors and a total registration of 7300 to the four-day convention at Dallas. Accordingly, there were 500 to 600 physicians at most sessions and at the opening session there must have been 800 doctors in the audience. In view of our Canadian potential, our own attendance by comparison is most encourag-

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ing when we get 600 to 800 doctors to the College conventions. At Dallas the A.A.G.P. had 86 scientific exhibits and nearly 300 technical exhibits.

To accommodate this great assembly, the A.A.G.P. with the Dallas group took over the vast Dallas Memorial Auditorium. The technical exhibits were entirely separate from the scientific ones, but it would be impossible to see more than a representative number of either during the four days. An hour's recess was provided morning and afternoon to view the exhibits but it was like trying to see all acts of a five-ring circus. However, the auditorium facilities were much more adequate than in even the largest hotel, and I believe we may have to use the same sort of convention site. Luncheons and ceremonial and social functions were held at a hotel in Dallas.

One aid to attendance was the fact that all general practitioners in the convention city and its immediate area were preregistered for the 1958 Scientific Assembly of the A.A.G.P.

The lectures began at noon on Monday and closed at noon on Thursday; this allowed physicians travelling from distant points to arrive and depart in time to embrace the whole program. Alternatively, it permitted a doctor to attend for the two middle days without missing more than six sessions.

Speakers for the sessions of the A.A.G.P. Assembly are selected largely on reputation and, in many cases, are paid an honorarium as well as expenses. The calibre of speakers was very high. Only one lecture is presented at a time so that there is no conflict of interest.

The American program provided no daily luncheon. Medical films were used in a way similar to our own practice. Closed-circuit television was not exploited to any extent. Monday night—opening night—of the four-day assembly was devoted to state chapter dinner meetings, which were mainly social in nature.

The A.A.G.P. held the business and committee meetings on the Saturday and Sunday preceding the convention, as we do. Their House of Delegates, which is patterned on the U.S. Senate and might be compared to our Board of Representatives, has 102 members and would be unwieldy were it not confined in functions, which are mainly to hear the committee reports and the presidential address. House sessions and committee meetings were held at a downtown hotel. To get through its agenda the House sticks strictly to Robert's *Revised Rules of Procedure*. There is a sergeant-at-arms, and everything is conducted in an extremely parliamentary manner. Virtually all the business of the American Academy of General Practice is thrashed out at committee meetings, and the printed reports of these meetings tabled at the House of Delegates' sessions arrive in large sheafs.

The annual dinner of the A.A.G.P. was held on the Tuesday night and the entertainment was quite fabulous. A feature worth noting was the practice of seating all nine past-presidents of the American Academy. They occupied a table immediately in front of and slightly below the head table and all were introduced.

Association Notes

MEETING OF THE EXECUTIVE COMMITTEE OF THE C.M.A.

The Executive Committee of the Caandian Medical Association met on Friday and Saturday, April 25 and 26, at C.M.A. House, Toronto. Their chief task was to review the reports of various committees to General Council; since these reports will be further commented on in the general summary of the proceedings of Council in our July 15 number, and subsequently published in full in the September 1 number, it is unnecessary to go into great detail here. Before considering these reports, however, the Executive Committe dealt with a number of other items of business.

It has previously been reported that the new system of payment of D.V.A. fees on the basis of 90% of the provincial fee schedule was involving physicians in certain provinces in financial loss, because of the low provincial tariff. A further examination of this question had suggested that the remedy was not to upset the general C.M.A. agreement with D.V.A., but rather to bring the provincial fee schedules in question up to a higher and more realistic rate.

The Executive Committee examined various methods for improving the liaison between members of the Federal Parliament and organized medicine. It was felt that all Members of Parliament required more information on the views of organized medicine, and on the basic reasoning behind these views. Methods of implementing this were discussed.

The Executive Committee debated matters of mutual concern related to Trans-Canada Medical Plans. An Ontario resolution that the C.M.A. should establish a separate standing committee on prepaid medical care with the following terms of reference: (a) to define, to bring up to date, and periodically review C.M.A. policy in respect to prepaid medical care; (b) to keep under review implementation of C.M.A. policy by the prepaid medical care plans and T.C.M.P., was discussed in full. It was finally decided that the C.M.A. Executive would set up a committee to review immediately the constitution and by-laws of T.C.M.P. and the functioning of that body within and without such constitution and by-laws, and to make any necessary representations to the T.C.M.P. Commission.

The Committee learned that one of the members of the C.M.A. nominated for the honourable status of Senior Member (Dr. A. S. Menzies of Morden, Manitoba) had died since his nomination. It was agreed that he be nominated to posthumous Senior Membership.

The arrangements for the annual meeting in Halifax, June 16-20, 1958, were reviewed and found very satisfactory. There is one unavoidable change in the arrangements. It had been hoped to have the premiers of Atlantic provinces as luncheon speakers at the meeting; however, a subsequent engagement has made it necessary for the premiers to be present in London, England, just before the meeting, and it is doubtful whether they will now function as luncheon speakers.

The arrangements for the annual meeting in Edinburgh, July 1959, were again reviewed. The selection of Canadian officers for this meeting is now complete

and the list of Canadian speakers almost complete. There are now over 3000 persons on the books of the official travel agency, University Tours Ltd., Toronto, and this number includes over 900 doctors. The problem of accommodation in Edinburgh need not be stressed. The question of a meeting of the Council of the Canadian Medical Association in 1959 on Canadian soil and possibly in relationship to the meeting of the Ontario Medical Association in Toronto in May was discussed. At Halifax this year, General Council will be asked to make a decision about this meeting, to state whether a meeting should be held, and to determine its time and place.

The need for a study of medical manpower in Canada was again debated, particularly in view of the divergent opinions on the adequacy or otherwise of the number of physicians now being graduated in the country.

The meeting of the new liaison committee between the Royal College of Physicians and Surgeons of Canada and the Canadian Medical Association on March 8 was reported and discussed. Some subjects which this liaison committee had dealt with were (1) the importance of a unified approach to government on behalf of the medical profession; (2) the consequences to medical education of the hospital insurance plan; (3) the inadvisability of ventilating intra-professional disputes in the lay press; (4) the type and content of a second year of hospital training designed to lead to the general practice of medicine; (5) certain applications of the Code of Ethics; (6) the all-Canadian program of hospital accreditation; (7) the supply of medical students. While on the subject of liaison with other bodies, the Executive Committee debated the question of an annual meeting between the Canadian Medical Association and its affiliate associations. This will be further explored.

The difficulty of holding the annual meeting of the C.M.A. in cities other than Toronto or Montreal was discussed and views for and against the centralization of the annual meeting in these two cities were expressed. A sub-committee will be set up to study this question further.

The Committee was shown plans for the construction of an additional wing at C.M.A. House, Toronto. Present accommodation has now reached saturation point, and further construction in the near future is necessary. The plan presented to the Committee was approved.

Applications for affiliation to the Canadian Medical Association were received and approved from (a) the Canadian Society of Laboratory Technologists, (b) the Canadian Nurses' Association, and (c) the Canadian Life Insurance Medical Officers' Association.

The Committee approved the proposals of the Canadian Joint Committee on Nursing made in connection with recommendations of the Canadian Conference on Nursing of November 1957, with the exception of one recommendation pertaining to methods of expanding the recruitment, selection and training of nurses for advanced studies. The Committee also went on record as approving the expansion of the experimental two-year basic nursing program which has already produced results in such centres as Windsor, Ontario. It has also stated to the Joint Committee its opinion that nurses during training should receive more adequate payment than is now the case.

The Executive Committee had been asked to sponsor a resolution on the testing of nuclear weapons, and a number of the Executive had also been asked to sponsor a private meeting of nuclear scientists. This led to a discussion on the radiological hazards of testing of nuclear weapons and other industrial and military uses of atomic energy. The Committee felt that its information on this difficult and complex field was quite inadequate for it to express opinions from the standpoint of organized medicine.

The second day of the meeting was devoted entirely to a consideration of reports of committees and individuals to General Council. The next meeting of the Executive Committee will be in Charlottetown on Friday and Saturday, June 13 and 14, 1958.

ANNUAL MEETING OF THE QUEBEC DIVISION

The Quebec Division of the Canadian Medical Association held their 20th annual meeting on Thursday, Friday and Saturday, May 1, 2 and 3, at the Hôtel Chantecler, Ste-Adèle-en-Haut. A registration of about 170 physicians enjoyed an excellent scientific program, and participated in social activities with their wives.

Scientific Program

The meeting opened with a brief address of welcome by the outgoing president, Dr. Georges Leclerc of Montreal. The Thursday morning scientific session began with a research paper by Dr. Charles W. Fullerton of Montreal General Hospital, who described the treatment of pleural effusion or ascites due to malignant disease by injection into the pleural or peritoneal cavity of nitrogen mustard. He had used this treatment in eight cases and had a successful response in four. He felt that cases most likely to respond were those in which the effusion was the only evidence of metastatic carcinoma, especially if the breast or ovary was the primary site of the tumour. The treatment is safe and inexpensive and in emergency can be given at home, the only side-effect being nausea.

Dr. E. H. Lehmann of Verdun Protestant Hospital discussed tranquillizers and other psychotropic drugs in clinical practice. He said that, in practice, the psychotropic substances could be classified as major (phenothiazine derivatives and reserpine) and minor, such as meprobamate. All these drugs have some side-effects and occasionally complications which may become dangerous. Any physician employing them should understand thoroughly the number and quality of these complications as well as their prevention and management. Although the drugs have had an almost revolutionary impact on therapy of psychotic conditions, they have been somewhat disappointing in treatment of neurotic anxiety, in which they play only an auxiliary role. Practitioners must familiarize themselves with the maintenance therapy of chronic psychotic patients released into the community.

Teaching symposia were arranged at luncheon both on Thursday and Friday. On Thursday there were two symposia, one on cardiac disease in which Dr. Jacques Genest of Montreal discussed the diet in hypertension and Dr. B. A. Levitan of Montreal dis-

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cussed hypotensive drugs in cardiac disease, and the other on traumatic surgery of the hand with presentations by Drs. F. M. Woolhouse and Yves Prévost.

The Thursday afternoon session began with Dr. T. J. Quintin of Sherbrooke in the chair, and a stimulating address by Dr. Marvin Lougheed of Montreal on radiation hazards, in which he remarked on the fact that the free-floating anxiety always present in the general population is now focused on radiology. He showed the futility of worrying about diagnostic radiology as a hazard, wisely pointing out that the cost of sufficient x-ray work to produce a genetic effect would be prohibitive.

Dr. Alan B. Noble of Montreal discussed anæsthesia in general practice, noting that there is no such thing as a minor anæsthetic and that the highest anæsthetic mortality might lie with the simplest cases. He felt that nobody should practise inhalation anæsthesia unless able to perform intubation. Early ambulation after inhalation anæsthesia he regarded as a myth. He recommended Xylocaine (lidocaine) as a local anæsthetic and remarked that premedication with barbiturates would lessen local anæsthetic reactions. He said that Pentothal should not be used in a dentist's office, and that relaxants should be used with great care and not to cover up inadequate anæsthesia.

Dr. L. Stanley James of the Presbyterian Hospital, New York, made a plea for rapid resuscitation of the newborn as a means of reducing perinatal mortality. Resuscitation included early suction of the respiratory tract with a simple apparatus, insertion of a plastic airway, stimulation by a sharp slap, and laryngoscopy followed by insufflation of oxygen into the trachea.

Dr. David R. Murphy of the Montreal Children's Hospital read a paper on surgical emergencies of the newborn, in which he discussed the varieties of intestinal obstruction and other malformations. Dr. H. F. Owen of Montreal stated that in timing pædiatric surgery two questions needed to be answered: (1) When would the child be most fit to withstand the mental and physical trauma of operation? (2) When would the anatomy of the structures be suitable for operation? Before operation, the child must be free of infectious disease, and its age and size be adequate; at the Montreal Children's Hospital a baby weighing 10 lb. and gaining weight was considered a reasonable risk. Timing of various surgical procedures was then discussed in detail. On Friday morning, with Dr. Renaud Lemieux of Quebec in the chair, the session opened with a description of oral hypoglycæmic agents by Dr. Allen Gold of Montreal. His results with tolbutamide were similar to those recorded elsewhere. He had also tried a new drug, phenylethyl diguanamide (PEDG); 15 patients had received the drug but in 10 cases it had to be abandoned because of nausea or anorexia. Other hypoglycæmic drugs were being developed, and making individual assessment even more important in diabetes.

Dr. Jean Sirois of Quebec gave an assessment of his results in 108 cases of subarachnoid hæmorrhage. Of the series 71 were cured and 24 dead while 13 had sequelæ. Mortality and morbidity were low in comparison with other series.

Dr. W. I. Card of Edinburgh, Scotland, discussed gastric secretion and peptic ulceration. He remarked that the acid-pepsin factor was not of equal importance in all types of ulceration, but was particularly important in duodenal and jejunal ulcer. He briefly discussed the inhibitory mechanisms of gastric secretion, and the nervous and hormonal secretory stimuli. He then discussed in greater detail the third variable affecting secretion, namely the secretory cell mass, applying the discussion to the treatment of peptic ulceration.

Dr. Claude E. Welch of Boston stated that hæmorrhage is the most difficult of the major complications of peptic ulcer to treat. Not only does it pose a problem of management, but it has a serious influence on prognosis afterwards. Patients with mild or moderate hæmorrhage should be treated medically, operation being carried out if there was repetition of hæmorrhage. With massive hæmorrhage, the patient would be admitted and given blood replacement; if bleeding stopped, the patient could be operated on later, but if it continued after five transfusions emergency surgery was indicated. Application of this plan at the Massachusetts General Hospital had meant that practically no patients below the age of 70 now died from hæmorrhage.

Saturday morning, with Dr. F. W. Fitzgerald of Lachute, the newly installed president of the division in the chair, began with a round table discussion on hæmatology. The moderator was Dr. E. H. Bensley of Montreal, and the members of the panel—Drs. D. L. Denton, G. Gosselin, and L. Long—discussed hæmolytic disease of the newborn, leukæmias and disorders of coagulation, respectively.

Dr. Bensley then gave an account of recent advances in toxicology. He dealt with the chelating agents, now firmly established in the treatment of lead poisoning and under investigation in treatment of poisoning with a variety of radioactive substances. He mentioned the use of penicillamine in Wilson's disease and its trials in lead poisoning and hæmochromatosis. He then mentioned the two schools of thought in treatment of barbiturate poisoning; one used stimulants and the other did not, but it was agreed that their use was only a small part of the treatment. Bemegride (Megimide) had been shown not to be a true antagonist to the barbiturates, as initially claimed. Dr. Bensley mentioned the poison control centres, of which 14 are now established in Canada and ten more in process of organization. The morning closed with a round table discussion of biliary tract disease with Dr. C. E. Hébert of Montreal in the chair and Drs. J. Bruneau, Card, Martin Hoffman and D. R. Webster as panellists.

On Friday at lunch there was a choice of two symposia: (1) a discussion of coronary heart disease by Dr. Paul David and Dr. Harold Segall of Montreal; (2) a discussion of burns treatment by Dr. H. J. Scott and Dr. M. A. Entin of Montreal.

Other Events

The annual meeting of the Quebec Division of the Canadian Medical Association was held on Friday afternoon, May 2. At this session, not only were the ordinary committee reports and other matters dealt with, but there were discussions of the hospital insurance scheme by Drs. J. Gilbert Turner of Montreal and Murray Douglas of Windsor, Ontario. Dr. Glenn Sawyer of Toronto described the Medical Secretaries' Association recently formed in Ontario, and the meeting concluded with the transfer of the chain of office from the outgoing president, Dr. Georges Leclerc of Montreal, to Dr. F. Walter Fitzgerald of Lachute.

Barcus Salmon

Dr. Morley Young, President of the C.M.A., has just transferred the chain of office from the outgoing president of the Quebec Division, Dr. Georges Leclerc, to the incoming president, Dr. F. W. Fitzgerald. From left to right: Dr. Leclerc, Dr. Young, Dr. Fitzgerald and Dr. Sylvio Leblond (President-Elect).

The annual banquet was held on Friday evening with Dr. H. Angus Bowes of Ste-Anne-de-Bellevue as guest speaker. He gave a witty address on the psychiatric aspects of high-fidelity, illustrated by musical selections. On Saturday, the closing luncheon meeting was addressed by Dr. Morley Young, president of the Canadian Medical Association.

SOCIAL EVENTS* AT THE 91st ANNUAL MEETING, HALIFAX, JUNE 16-20

Tuesday, June 17

Dinner to General Council—Nova Scotian Hotel.
6.30 p.m.—Reception, courtesy of N.S. Division.
7.30 p.m.—Dinner. Entertainment—musical program.
Dress: black tie.

Wednesday, June 18

Annual General Meeting—Nova Scotian Hotel.
8.15 p.m.—Installation of the President; presentation of awards.
9.30 p.m.—President's reception.
10.00 p.m.—Dancing.
11.00 p.m.—Buffet supper, courtesy N.B. Government.
Dress: Evening dress with decorations.

Thursday, June 19

Dalhousie Medical Alumni Association—Nova Scotian Hotel.
6.30 p.m.—Reception.
7.00 p.m.—Dinner.
Dress: Informal.
Don Messer and His Islanders—H.M.C.S. *Stadacona* (courtesy P.E.I. Division).
9.00 p.m.—Round and square dancing.
—Entertainment.
11.00 p.m.—Refreshments.

*These events do not include the luncheons held in the Nova Scotian each day of the convention week, or the interesting program planned by the Ladies' Committee.

MEDICAL MEETINGS

LA SOCIETE MEDICALE DE MONTREAL

La Société Médicale de Montréal held an all-day session on Saturday, April 26, 1958, in the Queen Elizabeth Hotel, Montreal. This was in fact the first medical convention that the new hotel had housed; in spite of this, arrangements for the meeting were perfect. The morning session took place with Dr. Albert Royer in the chair and consisted of three papers and a subsequent question period.

Dr. Gustave Gingras discussed the present and future position of rehabilitation, deploring the fact that it tended to be separated off from the rest of medicine and emphasizing that the efficacy of physical medicine was demonstrable at all stages of treatment. He specifically mentioned the progress made in rehabilitation in the province of Quebec. New centres were starting and more students of rehabilitation were in training; nevertheless all services were overwhelmed and many suitable cases had to be refused rehabilitation facilities for lack of personnel. Dr. D. P. Cyr of the Lahey Clinic, Boston, discussed splenectomy, combining his discussion with an analysis of a series of 258 splenectomies undertaken at the clinic. He said that the spleen was still a mysterious organ, although the surgery of the spleen had helped to reveal its functions. Diagnosis of splenic enlargement was usually made through a hæmogram or a myelogram, but sometimes after all studies had been exhausted the cause of splenomegaly remained unknown. In the Clinic series of 40 cases of idiopathic thrombocytopenic purpura, splenectomy had given good results in 77.5% of cases, with a mortality rate of 2.5%. Results of splenectomy had been excellent in all 35 cases of familial hæmolytic anæmia but much less satisfactory in acquired hæmolytic anæmia. Good results had been obtained in two-thirds of cases of splenomegaly with cytopenia; in congestive splenomegaly results of splenectomy had been much improved by addition of a splenorenal or portacaval shunt.

Professor E. Boltanski, of Paris, described himself as a gastroenterologist with a special interest in the psychosomatic aspects of his specialty. He emphasized the error in separating off functional from organic disorders. The main feature of the functional type of disorder of the digestive tract was its benign nature associated with lability. He noted the tendency for functional disorders to occur in introverts with no exteriorization of their aggressions. He also noted the association with peripheral circulatory disturbances. No explanation had yet been given for the vulnerability of these people to psychological trauma.

At luncheon, the chair was taken by Dr. Louis-Philippe Bélisle, president of the Society, and the luncheon speaker was Dr. C.-A. Martin, psychiatrist at the Roy-Rousseau Clinic, Quebec. Dr. Martin discoursed with charm on the general subject of alcohol, pointing out the sensation that would have been caused if alcohol had just been discovered as a tranquillizer in 1958.

The afternoon session began with a careful analysis of the criteria for the diagnosis of rheumatoid arthritis and of the role of steroids in the treatment of this disease, given by Dr. L. G. Johnson of McGill University. This was followed by a discussion of radical

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surgery for hepatic tumours by Dr. Alexander Brunschwig of Cornell University, who based his discussion on those cases in which major portions of the liver had been removed for malignant tumours. He pointed out that patients can carry on with only 20% of functioning liver; he also suggested that resistance to carcinoma may not be sufficient to overcome a large tumour, but may be sufficient to overcome small metastases after the major tumour has been removed.

The session ended with a paper by Dr. S. S. B. Gilder, editor of the *Canadian Medical Association Journal*, on "The Physician and the Mass Media of Communication" (press, radio, television), in which he discussed the C.M.A. code of collaboration with the press, and compared and contrasted it with relationships existing in France, Germany, Austria, Britain and the United States.

MONTREAL PHYSIOLOGICAL SOCIETY

The new, very modern and beautiful Main Hall of the Social Centre of the University of Montreal was the scene of the second all-day scientific meeting of the Montreal Physiological Society, held on Friday, March 7. Twenty-seven papers were presented. A buffet lunch, provided through the courtesy of Messrs. Charles E. Frosst & Co., was served in the Salon des Professeurs. For this reporter at least, the highlight was the Merck Lecture, presented by Dr. Leonard F. Bélanger, professor of histology and embryology, University of Ottawa. His subject was "Adventures in dynamic histology with radioactive sulphur". Professor Bélanger has achieved the enviable position where his scientific search is also his hobby—very aptly described in the title of his talk. He described the technique which he and Professor Leblond of McGill have developed—a histochemical procedure using autoradiographs—and the results of S^{35} incorporation into various tissue cells and the significance of these data.

V. W. Adamkiewicz and H. K. Uhthoff of the department of physiology, University of Montreal, pointed out that the usual commercial radiopaque substances are not satisfactory for visualizing blood vessels with a diameter smaller than 30 μ. These substances, when used at concentrations cited in literature, are in fact not opaque enough to visualize fine vessels. The difficulties can be avoided by using the x-ray opaque "Carbonyl iron", in a 60% w/v aqueous suspension. The "Carbonyl iron" is a powder with spherical particles of a mean diameter of 3 μ. The method has given very good results in experimental animals, is simple and requires no elaborate equipment. *Gaétan Jasmin and Pierre Bois* of the Department d'anatomie pathologique, Université de Montréal, described how the parenteral administration of the histamine releaser 48/80 in rats produces acute inflammatory reactions believed related to histamine release. In less than 24 hours, nearly all the glandular section of the stomach is necrotized. These lesions are reminiscent of the acute phlegmonous gastritis found in man in severe infection or intoxication or after an extensive burn. It is possible to desensitize rats to such gastric ulcerations after a short pre-treatment with histamine releasers (48/80 or polymyxine). It has been further observed that experimental alloxan diabetes, known to interfere with histamine release phenomena, also confers protection against the ulcer producing action of 48/80.

The gas exchange variations in chronic pulmonary diseases have received much attention but, surprisingly enough, very few studies have been done on arterial oxygen saturation, P_{O_2} and P_{CO_2} in emphysematous patients during exercise. *Charles Lepine, Roméo Soucy, M.-Jean Laberge, Jacques Lapalme and Fernand Grégoire* of the Institut Lavoisier, Montreal, have investigated 61 patients. In the whole group, the mean values for maximum breathing capacity, vital capacity, functional residual capacity and percentage ratio of residual volume to total lung capacity were: 51, 2.2 and 4.2 litres and 58.7%. During exercise, the mean minute ventilation and oxygen consumption varied from 6 to 16 l./m² and from 149 to 479 ml./m². The mean values for arterial oxygen saturation and P_{CO_2} showed a decrease, and the arterial P_{CO_2} an increase. All the variations were statistically significant.

A symposium on "infarctoid cardiopathy" was presented by *Hans Selye* and six of his associates of L'Institut de médecine et de chirurgie expérimentales, Université de Montréal. Following combined treatment with certain corticoids—especially with 2α-methyl-9α-chlorocortisol (Me-Cl-COL)—and electrolytes, infarct-like, massive myocardial necroses occur in a variety of animal species. This change has been called an "infarctoid cardiopathy" (because of its appearance) or an "electrolyte-steroid-cardiopathy" (because of the manner in which it is produced). Three factors appear to be involved: (1) the steroids—only steroids will do this, and cortisone (mineralocorticoid) is most effective, while glucocorticoid has very little effect; (2) the electrolytes—only sodium sulphate, phosphate and perchlorate appear to sensitize cardiac muscle to production of these lesions, the most effective inhibitors being calcium and magnesium; (3) stress—this is very non-specific. The ECG was registered, using the three standard leads, in the rat under light ether anæsthesia, before and after combined treatment with Me-Cl-COL and NaH_2PO_4. Decrease of heart rate and prolongation of PR and QT (QU) intervals, as well as lowering of T waves, were the most marked changes observed. All these changes were observed after only two days of treatment. However, after seven days of treatment, arrhythmia and conduction defects were detected.

B. Rose, A. H. Sehon and their associates of the Allergy Research Division, Royal Victoria Hospital, have prepared insoluble, antigenically specific polymers by coupling antigens (ragweed pollen extract, bovine serum albumin, human serum proteins) by stable azo bonds to polystyrene. These materials have been shown to absorb specifically the corresponding antibodies present in human allergic sera and in sera of immunized animals. Precipitating antibodies could be recovered from the adsorbents by lowering the pH to about 3. These isolated antibodies have been partially characterized by ultracentrifugal and electrophoretic analyses. The same authors presented a second report on the nature of the antibodies in ragweed-sensitive sera. It would appear that skin-sensitizing antibodies are associated with the fast-sedimenting serum components (S-19), that blocking

antibodies are associated with the slower sedimenting gamma globulins, and that both antibodies are responsible for hæmagglutination. The results of the other methods of fractionation will be reported.

The same enzyme system is involved in the glucuronvlation of N-acetyl-p-aminophenol (NAPA) and 17-hydroxycorticoids (17-OHCS), and both substances are excreted in the urine mainly as glucuronide. Conjoint administration of an adrenocorticosteroid and NAPA might therefore give rise to elevated and prolonged plasma levels of free 17-OHCS as a result of competitive inhibition. This was found to be the case, as reported by *W. Johnson and G. Corte* of the Research Laboratories, Frank W. Horner Limited. This suggests that elevated plasma levels of 17-OHCS, observed in patients receiving large doses of stilbœstrol or salicylates, may be due, at least in part, to inhibition of 17-OHCS glucuronylation.

The introduction of the orally effective hypoglycæmic agents tolbutamide and carbutamide has greatly stimulated investigation in carbohydrate metabolism, but their site of action has not been identified. *A. Gold and J. H. Darragh,* Queen Mary Veterans Hospital, told of their experience in over 100 diabetic patients. In approximately 65% of patients a hypoglycæmic effect adequate for treatment of the diabetes is obtained. Treatment failures may be subdivided into (a) those in whom no hypoglycæmic effect is demonstrated, (b) those in whom such an effect is obtained only in the presence of exogenous insulin, and (c) those in whom a hypoglycæmic effect inadequate for treatment is obtained. Experience with a new compound, D.B.I., indicates that the mode of action is probably different from that of tolbutamide. Evidence at hand suggests that these agents exert their hypoglycæmic effect at some site other than insulin, although insulin may enhance their action. In an attempt to correlate ketone metabolism with the clinical type of diabetes, the insulin requirements, nutritional status, incidence of degenerative complications, and the presence of infection, the concentration of blood ketones has been determined in 10 diabetic patients after withholding insulin, as reported by *J. H. Darragh and G. Joron* of McGill University Clinic and Montreal General Hospital. In the first group of 5 patients with maturity-onset diabetes, none had a history of ketoacidosis, but one patient with hæmochromatosis had a recent acute onset of diabetes with mild ketonæmia (15 mg. % total ketones, expressed as acetone). Insulin was stopped, and daily fasting blood samples were analyzed for glucose and total ketones. All developed hyperglycæmia, and in three patients there was no change in the blood ketones after five days without insulin. Two patients, including the patient with hæmochromatosis, developed a slight increase in blood ketones after three days (to 4 mg. %). Of the second group of five patients with growth-onset diabetes, all had a history of one or more episodes of ketoacidosis. No insulin was given for 24 hours before the test period. Breakfast was omitted, and blood samples were obtained every hour during the morning. The usual insulin was given before the noon meal. In two patients the initial blood ketones were normal, and there was no increase. Two patients had a higher initial level (5 and 7 mg. %), but there was no increase. One of these patients had an infected toe, and the other had severe diabetic retinitis, nephropathy and peripheral neuritis. In the fifth patient, who had been admitted to hospital during the previous week with moderately severe ketoacidosis, the blood ketones increased from 2 to 4 mg. % during the four-hour period.

Eleanor R. Harpur, Jessie Boyd Scriver, George Weber and F. W. Wiglesworth of the Montreal Children's Hospital presented interesting biochemical data on a child, 15 months old, with glycogen storage disease. Clinically there were hepatomegaly and growth failure. Enzyme studies of liver biopsy tissue showed that the enzymes associated with glycolysis were all increased, so that the child had no way of getting glucose for its tissues other than by mouth. Thus in this disease liver glycogen and acidosis increased because of constant glycolysis. Therapy consisted for the first six days of constant infusion of glucose; a diet was then given with glucose as the carbohydrate, no milk being given because of its galactose content, and no fructose. The child is doing well.

In a study reported by *M. Rosenfeld, J. Cross and K. A. C. Elliott* of the Montreal Neurological Institute, it was concluded that the drastic irreversible effects of brief cerebral anæmia on brain function cannot be ascribed to irreversible loss of aerobic or anaerobic metabolic activity. *Louis J. Poirier* of the histology and embryology department, Université de Montréal, presented studies on the nervous control of glycæmia exerted through two main neuro-endocrine mechanisms —the sympathetico-adrenaline and the vago-insulin systems.

L. J. Poirier and A. Beaulnes of the departments of histology and physiology, Université de Montréal, showed that all tranquillizers, except reserpine, can block effectively the hyperglycæmic responses to immobilization in the monkey. On the other hand, the hyperglycæmia produced by exogenous adrenaline is not presented by tranquillizers.

Pierre Bois and Gaétan Jasmin of the pathology department, Université de Montréal, described myocardial necroses observed in bilaterally nephrectomized water-restricted rats. Corticoid treatment greatly enhances these changes and produces widespread foci of myocardial necroses. Hypophysectomy as well as thyro-parathyroidectomy prevented the development of these myocardial necroses. *M. Saffran, Pamela Ward and Brigitte Zimmermann* of the Allan Memorial Institute of Psychiatry, McGill University, described studies on the corticotrophin-releasing activity of posterior pituitary preparations. *Guy Letellier and Louis-Philippe Bouthillier* of the department of biochemistry, Université de Montréal, presented data on the metabolism of γ-hydroxyglutamic acid-α-C^{14}-γ-semialdehyde in the intact rat. The effect of deficiencies of thiamine, riboflavin and pyridoxine on the pyrocatechol amine content of rat organs was described by *V. R. Woodford, Jr., B. D. Drujan, and T. L. Sourkes.* According to Holland and Schümann (1956), splanchnic stimulation increases the rate of synthesis and methylation of noradrenaline by the adrenal medulla. In a study on the release of catechol amines from the adrenal medulla of the cat during splanchnic stimulation, *N. R. Eade and D. R. Wood* of the department of pharmacology, McGill University, found that stimulation did not lead to extra amine formation. *N. van Gelder and K. A. C. Elliott* of the Montreal Neurological Institute reported on the distribution of

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exogenous gamma-aminobutyric acid in mammalian tissues. *B. Grad, J. Berenson and L. Caplan* of the Allan Memorial Institute of Psychiatry, McGill University, reported on the effect of thymus, bone marrow or kidney cells from pre-leukæmic AKR mice on the incidence of lymphatic leukæmia in $C3H_f$ X AKR F_1 recipients. *G. Weber and A. Cantero* of the Montreal Cancer Institute, Notre-Dame Hospital, reported on the absence of fructose-1, 6-diphosphatase activity in the Novikoff hepatoma. This appears to be a specific change in this tumour because no similar alteration was observed in various rapidly growing control tissues.

A. H. NEUFELD

CANADIAN ASSOCIATION OF PHYSICAL MEDICINE AND REHABILITATION

The Sixth Annual Meeting of the Canadian Association of Physical Medicine and Rehabilitation will be held in the Committee Room (second floor) of the Château Frontenac, Quebec, June 12-14, 1958. At the opening session on Thursday, June 12, the following papers will be given: "Clinical Aspects of Electromyography"—Max Newman, Detroit; "Rehabilitation in Quebec City"—Maurice Delage, Quebec City; "Shoulder Pain and its Management"—John S. Crawford, Toronto; "The Canadian Hip Disarticulation Prosthesis" (film)—John Fowler, Edmonton; "A Hemipelvectomy Prosthesis"—Edgar Lepine, Montreal; "Rehabilitation of Paraplegic Amputee" (film)—M. G. Peter Cameron, Saskatoon; "Experimental Evaluation of Muscle Replants in Spastic Conditions"—T. E. Hunt, Saskatoon; "Geriatric Problems in Rehabilitation"—Benoit Boucher, Quebec City. At 7.30 p.m. on this day a visit and reception has been arranged at the Quebec Workmen's Compensation Commission, 225 Grande Allée, Quebec City.

On Friday June 13, at 11.30 a.m., a visit to La Clinique de Réhabilitation de Québec, Inc., has been arranged, followed in the afternoon by further papers: "Review of Cerebral Palsy Cases"—G. Gingras *et al.*, Montreal; "An Aphasia Rehabilitation Clinic"—Charles M. Godfrey, Toronto; "Aids to Rehabilitation"—M. H. L. Desmarais, Winnipeg; "Low Back Pain"—Jean-Louis Larochelle, Quebec City; "A Report on Studies of Spinal Traction"—G. A. Lawson and C. M. Godfrey, Toronto. At 6.30 p.m. a banquet will be held in the Riverview Room, Château Frontenac (dress formal). The guest speaker will be Mr. G. E. Halpenny, Parliamentary Assistant to the Minister of National Health and Welfare, Ottawa.

On Saturday June 14, the following papers will be given: "The Hand Splint—An Office Procedure"—Joseph Berkeley, Windsor; "Prosthetic Aids for Upper Extremity Disabilities"—G. Gingras, V. Susset and C. Corriveau, Montreal; "Appliance Research in Saskatchewan" (illustrated by films and slides)—Adrian C. Kanaar, Regina; "Physical Medicine in the National Health Scheme in Britain"—Frank Cullis, Regina.

The ladies' program will include on Thursday, June 12, a visit and reception at the Quebec Workmen's Compensation Commission, and on Friday a visit to Ste-Anne-de-Beaupré shrine and Montmorency Falls, with luncheon at Manoir St-Castin, Lac Beauport, after which a sightseeing tour of Quebec City has been arranged.

THIRD CANADIAN CANCER RESEARCH CONFERENCE

The Third Canadian Cancer Research Conference will be held at the Delawana Inn, Honey Harbour, Ontario, from June 15-19. It is sponsored by the National Cancer Institute of Canada in affiliation with the Canadian Cancer Society.

The first day of the scientific program, Monday, June 16, will be devoted to papers on nucleic acids. The morning session will include papers on function, metabolism, and histological localization of desoxyribonucleic acid by workers from New York, Vancouver, Montreal, Saskatoon, and Bethesda, Maryland. At the evening session Dr. J. H. Quastel of Montreal will be in the chair and there will be further papers from Saskatoon, Montreal, Halifax, and the University of Illinois.

Tuesday will be devoted to papers on genetics and cancer. At the morning session, the chair will be taken by Dr. J. Doupe of Winnipeg; there will be papers on genetic factors involved in the development of and susceptibility to cancer, on etiology of leukæmia, and on chromosome changes in tissue culture. At the evening session, chaired by Dr. Carlton Auger of Quebec, Dr. G. Klein of the Caroline Institute, Stockholm, Sweden, will read a paper on "Variation and Selection in Tumour Cell Populations".

On Wednesday, June 18, there will be a discussion of viruses and tumours with papers from the University of Illinois, Bethesda, Maryland, and Toronto. The evening session will include papers from Montreal, Boston and England (by Dr. J. F. Loutit of the Radiobiological Unit, Harwell).

The last morning will be devoted to the biology of cancer. Dr. C. L. Ash of Toronto will be in the chair and papers to be read include contributions from Dr. L. H. Gray of the Mount Vernon Hospital, Middlesex, England, and Sir Macfarlane Burnet of Melbourne, Australia.

CANADIAN ASSOCIATION OF PATHOLOGISTS

The Canadian Association of Pathologists have arranged for a series of Science Sessions to take place in the Auditorium, Camp Hill Hospital, Jubilee Street, Halifax, Nova Scotia, on Friday and Saturday, June 20 and 21.

The sessions will be as follows:

Friday morning, June 20 (chairman, Max Klotz): "Membranous Glomerulonephritis—A Biopsy Studied by Light and Electron Microscopy"—Henry Z. Movat, Toronto; "Histoplasmosis Endocarditis"—Robert H. More, M. Daria Haust and G. Wlodec, Kingston; "The Pathogenesis and Evolution of the Metaphysical Cortical Defect of the Bones"—J. Pritchard, Montreal; "Co-existent Ovarian and Endometrial Adenoacan-

thomas"—James S. Crawford and Pierre Fournier, Ottawa; "The Armed Forces Institute of Pathology"—Capt. W. M. Silliphant, U.S. Navy, Director; "Histopathological Variations in the Diagnosis of Breast Lesions"—D. Magner and A. J. Phillips, Ottawa; "Carcinoma of Apocrine Glands"—G. F. Kipkie, Kingston; Progress Report of National Research Council Committee on Hospital Infections—D. H. Starkey, Montreal.

Friday afternoon (chairman, C. M. Harlow): "Pathology of Experimental Asphyxia and its Relation to Sudden Death in Infancy"—Christopher P. Handforth, Halifax; "Vasculitis in Man"—Professor H. E. MacMahon, Boston, guest speaker; "Virus Meningitis in the Atlantic Provinces"—C. E. van Rooyen and R. C. Dickson, Halifax; "Nutritional Factors in Experimental Mouse Hepatitis"—Boris Ruebner and James Bramhall, Halifax; "Hyaline Glomeruli in the Newborn"—Norbert Kerenyi, Halifax; "Marine Oils and Cholesterol Metabolism"—C. M. Harlow, Halifax.

Saturday morning, (chairman, Prof. John MacGregor): "Carcinoma *in situ* in Great Britain"—Claude Taylor, Birmingham; Seminar on Biopsies for Diagnosis—A. H. Bird, Saint John.

Business meetings will follow these two sessions. On both days, luncheon can be obtained at Camp Hill Hospital and will be served at 12.30.

L'ASSOCIATION DES ANATOMO-PATHOLOGISTES DE LA PROVINCE DE QUEBEC

Le congrès annuel de l'Association des Anatomo-Pathologistes de la Province de Québec (Quebec Association of Pathologists) aura lieu les vendredi et samedi 6 et 7 juin prochains, dans le nouveau pavillon de la Faculté de Médecine de Laval, dans la Cité Universitaire de Ste-Foy. Renseignements: Dr Robert Garneau, Institut d'Anatomie Pathologique, Université Laval, Québec, Qué.

CANADIAN DIABETIC ASSOCIATION

The 1958 scientific medical session of the Canadian Diabetic Association will be held in the Public Health Clinic, Halifax, N.S., on June 17, from 2 to 5 p.m. The program is as follows: "Renal Complications of Diabetes"—Dr. Guy E. Joron, Montreal; "Experimental Diabetes and Nephrosis"—Dr. N. Kalant, Montreal; "Tolbutamide" (round table discussion)—Dr. A. Gratton, Montreal, Dr. W. T. W. Clarke, Toronto, and Dr. Irwin Hilliard, Saskatoon; Panel discussion: "When, Where, Why, How to use Insulin in Diabetes"—Dr. B. S. Leibel, Toronto, Dr. J. C. Rathbun, London, Ont., Dr. R. C. Dickson, Halifax, and Dr. D. R. Wilson, Toronto. Dr. G. B. Wiswell is chairman of the Program Committee.

LETTERS TO THE EDITOR

MUNCHAUSEN SYNDROME

To the Editor:

Dr. Shane is to be commended for introducing the Muenchhausen (anglicized to Munchausen) syndrome to your readers (*Canad. M. A. J.*, 78: 532, 1958) since every doctor may be the "victim" of such patients.

There have been extensive discussions about this syndrome, particularly in some medical journals in England, but Dr. Shane's presentation is so clear that there is no need to make further comments. However, I want to object to the eponym because it is misleading. Baron Muenchhausen, who is still alive in the memory of many generations as a source of refreshing phantastic humour, is the prototype of pseudologia phantastica with his apparently purposeless duels and harmless romancing. The fact that there are deep-seated psychopathologic reasons for his narrations does not matter in this context. On the other hand, the "perennial peregrinating problem patient" is a sociopathic personality, unable to identify himself with society and its laws but at the same time abusing its institutions. Although the syndrome has been well known for decades in many countries of continental Europe, it has not been officially labelled. However, in clinical jargon it has been given various names, most of them being of a facetious nature, e.g. "frater hospitalis".

I think that the denomination of the syndrome should be revised before it becomes a permanent heading in future textbooks of psychiatry.

M. TYNDEL, M.D., Ph.D.
459 Bloor Street West,
Toronto, Ont.,
April 28, 1958.

PULMONARY THROMBOSIS OR EMBOLISM?

To the Editor:

I read with great interest the Louis Gross Memorial Address given by Dr. Fleischner entitled "Pulmonary Embolism" (*Canad. M. A. J.*, 78: 653, 1958).

Dr. Fleischner should be congratulated for advocating again that we should all continue to be "thrombosis-minded" in the postoperative period. I feel, however, that we must question his statement that "if pulmonary infarction is diagnosed by clinical means or roentgenologically, this signifies that there has been an episode of embolism", for on this statement of the etiology of pulmonary infarction may rest the treatment.

Cummine and Lyons carried out some work on postoperative intravascular thrombosis in the Department of Surgery, University of Sydney, which was presented as a Hunterian Lecture[1] by Professor Dew. These workers said that "involvement of the veins of the lower limb only occurs on the average in about 50% of cases of pulmonary clotting", and they believed that "intravascular thrombosis not only can occur in the lungs as a primary phenomenon but this is much more common than is usually thought. Post-

operative thrombosis does occur not only in the lower limbs but in the lungs, in the brain, in the heart and sometimes in the mesentery". Should not consideration be given to their work before perpetuating the use of the term "pulmonary embolism" for all these types of case? For no other diagnosis than primary pulmonary *thrombosis* can explain those cases with sudden onset, in the postoperative period, of dyspnœa with cyanosis and tachycardia, in the absence of toxæmia and deep venous thrombosis in the legs, and with bilateral basal radiological signs which simulate bronchopneumonia.

This being the case, that primary pulmonary thrombosis is the etiological factor in many cases of pulmonary infarction, then interruption of the peripheral veins as a method of preventing further "embolic" attacks is valueless as an attack upon what is a general blood abnormality, apart from the fact that the operation very frequently cripples the patient for life.[1, 2]

It is suggested that when a pulmonary infarct is diagnosed it does not necessarily signify that there has been an episode of embolism.

W. N. COOMBES, M.B., F.R.C.S.

422 Fraser St.,
North Bay, Ont.,
May 4, 1958.

REFERENCES

1. DEW, H.: *Ann. Roy. Coll. Surgeons England*, 13: 1, 1953.
2. MURLEY, R. S.: *Ibid.*, 6: 283, 1950.

THE PARABLE OF EACH AND ALL

To the Editor:

May I use your column to convey to Dr. C. P. Harrison my appreciation of his delightful contribution "The Parable of Each and All" (*Canad. M. A. J.*, 78: 725, 1958). It reads like a Kahlil Gibran and was a refreshing change from the usual letter or report.

Medical Arts Bldg.,
Hamilton, Ont.,
May 3, 1958.

GORDON MACFARLANE, M.D., F.R.C.S.[C.]

THE LONDON LETTER

(From our own correspondent)

POLIO VACCINE SHORTAGE

The Ministry of Health's policy on poliomyelitis vaccination is a near-perfect example of how not to do it. Last year the Minister consistently refused to supplement local supplies by imports of Salk vaccine from Canada and the United States—mainly on the grounds that Canadian and American standards of safety did not comply with British standards. Then, suddenly and almost overnight, it was announced that sufficient supplies were to be imported to allow certain priority classes—children under 15 and expectant mothers—to be vaccinated before the 1958 poliomyelitis season. Parents were urged to register for this life-saving measure, and local authorities and family doctors were instructed to take all the necessary steps to ensure that this campaign should be put into force forthwith. Local authorities, general practitioners and parents are all now set for this mass vaccination—but the Minister is unable to provide the vaccine. Some 6½ million doses are required to carry out promises, but only 2 million have been delivered. According to the Minister of Health, in a statement to the House of Commons, everyone is to blame except his Ministry—the two British firms, the Canadian and the American firm, which were to supply the vaccine, have all let him down.

This is a most curious coincidence, but what is worrying everyone is not so much the coincidence but the promises which the Minister has made in the past, for which there can be no conceivable justification. His major mistake has been that he has never made it clear to the country that no-one can possibly guarantee a given amount of poliomyelitis vaccine by a given date. If Ministers will dabble in such matters, it is being said, they should really make certain of their facts before they make promises to the public.

REGIONAL MORTALITY

Why is the suicide rate in Wales only three-quarters of that in England? Why are deaths from leukæmia one-and-a-half times as high in the south as in the north of England? Why is there such a striking inverse relationship as regards deaths from cancer of the breast and cancer of the uterus between the north and south of England? In the north the former is low and the latter high in frequency, whereas the converse holds true in the south. These are some of the many intriguing questions raised by the recently published Registrar General's analysis of area mortality in England and Wales. Among the many other interesting points in this analysis is the fact that in the cotton towns of Lancashire the death rate among women is 23% above the national average. This may well be correlated with the fact that their death rate from bronchitis is more than twice the rate for women in the country as a whole. This high incidence of fatalities from bronchitis applies to the north of the country as a whole, compared with the south. Thus, the probability of dying from bronchitis is twice as high in the north-west as in the south-west. Some of the differences seem to have a relatively simple explanation—e.g. that deaths from peptic ulcer are low in rural areas—but why should Wales have a higher death rate than England from cancer of the stomach and hyperplasia of the prostate? Optimistically, one hopes that somewhere in this mass of carefully collected and collated data there may be some clue to some of the many etiological problems of present-day medicine.

SMOKING IN CINEMAS

Great Britain is one of the few civilized countries of the world that allows smoking in cinemas and theatres, and, in spite of repeated protestations on the part of the public authorities—local and national—that everything possible is being done to discourage excessive smoking, there is no evidence that any of them are prepared to take this very obvious step towards discouraging the habit. All the more credit is therefore due to the London cinema circuit that, as an experi-

ment, decided to forbid smoking in three of its cinemas on two nights in the week. Alas, this commendable experiment has had to be abandoned after six months because the cinemas in question were getting the reputation of being permanently in the "no smoking" category, and the decline in business was more marked than in other cinemas owned by the company.

Smokers' Clinics

An even more interesting reaction to the carcinogenic cigarette scare is the almost revivalist fervour with which the first smokers' clinic of the National Society of Non-Smokers has been greeted in Liverpool. So great has been the response that the society has had to stop advertising it as they cannot cope with the numbers who wish to attend. These have completely swamped the hotel room in which the clinic was first held, and a hall has had to be rented for the purpose. A second clinic is to be opened in London this month. The treatment at these clinics is given in three instalments. First there is general psychotherapy for groups of up to a dozen people at a time. There is then a personal interview with the doctor, and, finally, after an interval of a week or two, a return visit to the clinic to report progress.

William A. R. Thomson.

London, May 1958.

ABSTRACTS *from current literature*

MEDICINE

Pleural Biopsy in Etiologic Diagnosis of Pleural Effusion.
R. F. Donohoe, S. Katz and N. J. Matthews: *Ann. Int. Med.*, 48: 344, 1958.

The literature on pleural biopsy is briefly reviewed, and the advantages of employing this procedure in the study of pleural effusion are discussed. The results of 132 pleural biopsies are presented, and the surgical and aspiration methods are compared. It is concluded that aspiration biopsy is the initial method of choice and should be employed early in the course of the effusion—routinely at the time of the initial thoracentesis. Surgical biopsy, with or without total exploration, should be reserved for those in whom aspiration biopsy has not proved rewarding. Both tuberculosis and malignancy may be present and yet the pleura demonstrate only non-specific changes.

Patients in whom tuberculosis is suspected as the cause of a pleural effusion should not be subjected to long-term chemotherapy, with all its implications, without confirmation, which preferably should be obtained early. If this cannot be accomplished by conventional methods, including aspiration biopsy, then surgical biopsy should be undertaken. A frozen section of pleura should be obtained through an intercostal approach and, if inconclusive, full exploratory thoractomy is then warranted. The authors consider that an entity of pleuritis due to an undetermined agent probably exists which, in its clinical manifestations, is not too dissimilar to its pericardial counterpart, idiopathic benign pericarditis.

S. J. Shane

Patent Ductus Arteriosus in Association with Pulmonic Stenosis.
D. C. Heiner and A. S. Nadas: *Circulation*, 17: 232, 1958.

All of six children with the combination of patent ductus arteriosus and pulmonic stenosis were found, in addition, to have several noncardiac anomalies, including mental retardation, microcephaly, congenital cataracts, nystagmus, retinal degeneration, strabismus, and deafmutism. The identity of these anomalies with those seen in offspring after pregnancies complicated by rubella is suggestive of a common etiologic factor. The gestation of at least two of these patients was complicated by known rubella. The coexistence of patent ductus arteriosus and pulmonic stenosis is usually recognizable clinically without angiocardiograms or cardiac catheterization. This combination of defects should be considered in patients with the diagnosis of either patent ductus arteriosus or pulmonic stenosis resulting from a pregnancy complicated by rubella, or in the presence of noncardiac defects of the type described. The clinical profile also includes delivery at full term with less than usual birth weight, a murmur audible in early infancy, and slow weight gain and linear growth. Cardiac examination usually reveals a wide pulse pressure, a continuous murmur in the second left interspace, and a separate rough systolic murmur and thrill maximal in the pulmonic area and suprasternal notch, with good transmission to the neck and back. Electrocardiograms show right ventricular hypertrophy or incomplete right bundle-branch block, sometimes in combination with left ventricular hypertrophy. Radiologic examination shows moderate cardiomegaly involving both ventricles and usually the left atrium, with engorged pulmonary vasculature. Division of the patent ductus is recommended in each instance. Patients with evidence of a significantly increased right ventricular work load should have preoperative cardiac catheterization to determine the need for simultaneous valvotomy.

S. J. Shane

The Nitrous Oxide Test: An Improved Method for the Detection of Left-to-Right Shunts.
A. G. Morrow, R. J. Saunders and E. Braunwald: *Circulation*, 17: 284, 1958.

In the past, the detection of intracardiac and extracardiac left-to-right shunts has been based upon differences in the oxygen content of blood obtained from the venæ cavæ, right atrium, right ventricle, and pulmonary artery. Since relatively large differences in oxygen content may exist in these areas in subjects without shunts, the oxygen method sometimes provides inconclusive or even misleading diagnostic information. The inhalation of nitrous oxide, an inert foreign gas, and the subsequent measurement of its concentration in arterial and right heart blood provides a new diagnostic approach in which the difficulties inherent in the oxygen method are largely obviated. This communication presents the theory, technique, and diagnostic applications of the nitrous oxide test, and a comparison of the nitrous oxide and oxygen methods in the detection of left-to-right shunts.

In 41 of 43 patients with proved shunts at the atrial level, the ratio of right atrial to arterial nitrous oxide content (RA/A) exceeded 31%, the highest value observed in 83 control patients. In all 24 patients with proved shunts the ratio PA/A or RV/A exceeded

20%. The highest PA/A or RV/A ratio in 58 patients without shunts was 16%. The nitrous oxide test was distinctly superior to the oxygen method. In 149 patients in whom both tests were performed, there were 22 diagnostic errors on the basis of oxygen differences and three errors with the nitrous oxide test.

S. J. SHANE

Myocardial Infarction: Its Racial Incidence in Cape Town during 1956.

V. SHRIRE: *South African M. J.*, 32: 177, 1958.

The author analyzed 4147 electrocardiograms taken in 1956 on adults over the age of 19. The patients had the following distribution: European 2394, coloured 1539, and Bantu 314, with a ratio of 1.2 to 1 between European and non-European. The total number of infarcts was 336, with a ratio of 3 to 1 between the two groups. If less rigid criteria were used, the percentage of races in 645 patients with myocardial infarcts was: European 73.2, coloured 26.75, and Bantu 0.15. These findings confirm the extreme rarity of myocardial infarction in the Bantu as well as its higher incidence in the European than in the Cape coloured.

W. GROBIN

Clinicopathologic Correlations of Renal Biopsies in Hypertension with Pyelonephritis.

J. C. MERRIAM, S. C. SOMMERS AND R. H. SMITHWICK: *Circulation*, 17: 243, 1958.

Renal biopsies from 120 cases of hypertension taken during sympathectomy were diagnosed pathologically partly as chronic pyelonephritis. Clinical comparisons were made with a larger series of hypertensive patients whose biopsies did not demonstrate pyelonephritic infection. The pyelonephritic series had a somewhat increased mortality and significantly higher average diastolic blood pressures for the same grades of arteriolar sclerosis, and did not show as frequent improvement of impaired kidney function postoperatively as the purely nephrosclerotic group. Approximately one-third of each series responded with a lowering to normal levels of the diastolic blood pressure after sympathectomy, and nearly one-half showed a postoperative improvement in the hypertensive retinopathy.

S. J. SHANE

SURGERY

Venous Thrombosis of the Lower Limbs with Particular Reference to Bed-rest.

N. M. GIBBS: *Brit. J. Surg.*, 45: 209, 1957.

An exhaustive review of the present knowledge in the field of thrombo-embolism accompanies an impressive list of cases examined by a pathologist. Practically all pulmonary embolism comes from lower limb veins. More cases come from medical wards than from surgical. Slowing of the blood flow in leg veins is to be prevented if possible, but the position assumed by a patient in bed in hospital and the unnecessary immobilization for doctors' and nurses' convenience and tidiness block improvement.

The site of thromboses in valve pockets of leg and thigh veins, the vague symptoms and signs of clinical thrombosis, and the occasional relationship to local injury all confirm the findings of previous investigators.

BURNS PLEWES

Surgical Experiences in Treatment of Aneurysms of the Thoracic Aorta.

F. H. ELLIS, JR., J. W. KIRKLIN AND A. J. BRUWER: *Surg. Gynec. & Obst.*, 106: 179, 1958.

Because of the almost uniformly short interval between diagnosis and death in cases of untreated thoracic aneurysms, surgical intervention is now indicated in most instances. This paper deals with a study of 20 patients, ranging from 5 to 71 years, who underwent surgery. Aneurysms are classified in order of frequency as: arteriosclerotic, syphilitic, traumatic, congenital, mycotic and dissecting. The various types are illustrated in an interesting collection of photographs, so that the article is worthy of study.

The majority of the arteriosclerotic lesions were fusiform and involved the aorta distal to the left subclavian artery. Although the classical location for luetic aneurysms is the ascending aorta, in this group of cases they were also noted to arise distal to the left subclavian. Those due to trauma are said to occur with greatest frequency just distal to the left subclavian and just above the aortic valve.

The usual symptoms were pain and thoracic discomfort, cough, dyspnœa, hoarseness and dysphagia. Routine sheet plates may be very revealing and warrant careful scrutiny. Special views including angiocardiographic technique are important as an aid in differentiating from mediastinal tumours. Such signs as erosion of the vertebral bodies or deviation of the œsophagus on lateral projection after barium swallow must not be overlooked. The type of incision was varied for the individual case. If necessary, as for example in a lesion of the ascending aorta and aortic arch, bilateral anterior thoracotomy through the third or fourth intercostal space with division of the sternum was employed.

The problem of spinal cord ischæmia was circumvented in most cases by the use of hypothermia, although in one patient a bovine shunt was employed while the patient was operated on under normothermic conditions.

The additional burden placed on the heart is another hazard of clamping the aorta. The average body temperature in these hypothermic cases was 30° C. although it is agreed that 32° C. would be safer. This, it is felt, allows up to one hour of aortic occlusion with minimal danger of spinal cord ischæmia.

Homologous aortic grafts were used in all but two instances, where Ivalon was tried. Fifteen of the patients explored had a resection and five of these died in hospital, a mortality rate of 33.3%. Although this may seem a very high price to pay, it is also an indication of what progress has been made in this heroic surgical field. Moreover, it is certain that as time goes on these figures will show considerable improvement.

A. M. DAVIDSON

Aspiration Biopsy of Breast Tumours.

ANNE GIBSON AND GWENDOLINE SMITH: *Brit. J. Surg.*, 45: 236, 1957.

The use of aspiration biopsy with a syringe and an 18-gauge needle is recommended for biopsy of breast tumours, both in the operating room and before irradiation in inoperable carcinoma. The Dudgeon technique for cell diagnosis is used. It is suggested that there is less danger of spreading the tumour and that

by this method carcinoma of the breast treated first by radiotherapy can be followed up more accurately.

Negative results must be accepted with caution if the case is clinically malignant. In 41 cases in which the clinical diagnosis was not certain before operation, the correct answer was given in 36. The other five cases showed benign cells only on aspiration but carcinoma was present—no unnecessary mastectomies were done. BURNS PLEWES

Comminuted Fractures of the Lower End of the Radius.
O. C. HUDSON AND T. J. RUSNACK: *Am. J. Surg.*, 95: 74, 1958.

Because of the radial shortening and deviation that occurs when these fractures heal, resection of the distal one inch of ulna is advocated. This article is a follow-up report on 25 of these cases, in which the author claims superior results for the majority. Ten patients had absolutely no complaints and considered the wrist as good as before the injury.

Others had varying degrees of subjective and objective findings. In some instances gross alteration of the normal volar and ulnar tilt of the radial articular surface was noted without untoward effect. In this series good results were totally lacking with regenerated ulna, which is contrary to the experience of some authorities who claim that best results are obtained when the process of regeneration is active.

The operative treatment consists simply of subperiosteal resection of the distal one inch of ulna. Closed reduction is carried out on the radius, after which a long arm cast is applied with the forearm in full supination. The importance of early finger movements postoperatively and continuing throughout the 10 to 12 weeks of immobilization is stressed.

A. M. DAVIDSON

Treatment of Acute Obstruction or Perforation with Carcinoma of the Colon and Rectum.
J. C. GOLIGHER AND F. G. SMIDDY: *Brit. J. Surg.*, 45: 270, 1957.

This is a study of 405 cases of carcinoma of the colon and rectum complicated by perforation or obstruction, or both. The total number of colon tumours seen at the General Infirmary at Leeds was 1644 of which 17.6% were obstructed and 7.0% were associated with perforation. Though left-sided malignant tumours were most often the cause of obstruction, they are much more common, and right colon tumours caused obstruction almost as often in proportion to their frequency. Rectal lesions rarely caused acute obstruction.

Most left colon obstructions were operated upon, but the mortality rate following the Paul-Mikulicz resection was high. The results of cæcostomy were not as good as transverse colostomy, showing a mortality rate of 50% as compared to 17%.

Patients with right colon obstructions seemed to survive right hemicolectomy just as well as the palliative ileo-transverse colostomy. In fact, 44% of the acute obstructing tumours were resected, as compared with a resection rate of 48% for the whole group with or without obstruction.

Perforation as a complication of carcinoma of the colon and rectum occurred often through a stercoral ulcer, usually in the cæcum. But in twice as many the perforation was at the side of the tumour. Occasionally the cancer obstructed the appendix, causing appendicitis with perforation. Perforation due to obstruction resulted in a mortality rate of 90%. The two survivors out of 20 had an immediate hemicolectomy and a suture with proximal colostomy.

All the patients with perforations not operated upon died. Suture of the perforation and colostomy was fatal almost as often. The best results followed primary colectomy, usually right-sided; 16 out of 21 got better.

A high proportion of patients who survived the perforation or acute obstruction later had a radical resection of the tumour. BURNS PLEWES

Contiguous Skin Replacement with Particular Reference to the Rotation Pedicle.
R. G. LANGSTON: *Am. J. Surg.*, 95: 294, 1958.

This brief review cannot be done justice in an abstract and is best consulted for details of the methods used for closing defects, especially by rotation flaps. Although it is essential that the plastic surgeon be ingenious, imaginative and ready to modify various alternatives, the procedure he uses must be based on certain fundamental principles.

Adjacent skin will often give the best cosmetic results if it is possible to utilize it without jeopardizing the blood supply. If not, a free graft or distant pedicle may be utilized satisfactorily. It is imperative to consider carefully where the blood supply will come from, and also to ensure that the suture line will not be under undue tension. A pattern of the defect to be covered is very useful. We are reminded that inadequate venous return may be just as disastrous as poor arterial supply.

The rotation flap is of great value in repair of the face. There are different variations but probably one of the most useful is the Abbé-Estlander, where the full thickness skin and mucous membrane is rotated 180 degrees to close a defect about the mouth. If necessary, these may be supplemented with submandibular, preauricular or cervical flaps.

The tremendous advantage that the rotation flap has given in the past decade to closure of decubitus ulcers is referred to. By this means, sometimes with concurrent removal of underlying bony prominences, thick durable skin is moved over the weight-bearing area. A. M. DAVIDSON

THERAPEUTICS

The Significance of Exogenous and Endogenous Factors in Growth of Malignant Neoplasms *(In German).*
C. HACKMAN: *Deutsche med. Wchnschr.*, 83: 134, 1958.

Malignant neoplasms do not grow completely autonomously; they are subject to a variety of stimulating and inhibiting influences. The authors give a well-documented review of these influences and the possibilities of promoting or suppressing their effects. Therapy aims at eliminating growth-stimulating factors and promoting growth-inhibiting factors. The stimulating factors are: (1) growth-promoting impulses originating in the tumour itself, which can be removed by surgery; (2) damage to the body's defences, for example, by radiation, faulty diet (high protein and fat), and endocrine and other factors damaging the reticulo-endothelial system.

Growth can be inhibited by administration of cytostatic chemicals and by attempting to improve the

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body's defences. Resistance can be enhanced by exposure to certain infections and through administration of tumour antigens. These are desoxyribonucleoproteins, which are thermolabile and water-soluble and are found within the cell nuclei. Active immunization has produced remarkable stimulation of defence against tumours in animal experiments. Active immunization in man is not possible in the presence of cancer, and prophylactic vaccination is at present of problematic value. Southam and Rhodas are quoted as reporting inoculation with human tumour material in volunteers, and finding a marked difference in the reaction to the inoculation in cancer patients and healthy persons. Sarvinal (Bayer), which is a purified extract from organs of animals that have been highly immunized against tumours, has been available to the German medical profession for experimental purposes for some time. Its value as an adjunct to present methods of treatment and in the intervals between x-ray or chemotherapy courses should be great, particularly as it is completely free of toxic side effects.

W. GROBIN

Prednisolone Aerosol in Asthmatic Bronchitis.

G. A. PETERS AND L. L. HENDERSON: *Proc. Staff Meet. Mayo Clin.*, 33: 57, 1958.

Prednisolone phosphate in the form of a solution can be nebulized satisfactorily and appears to be well tolerated by inhalation. Ten of 11 asthmatic patients derived benefit from treatment with this preparation. This form of therapy may prove a useful adjunct in the management of asthma, and merits further trial for a more definitive evaluation. S. J. SHANE

INDUSTRIAL MEDICINE

Impact on Medicine and Industry of Use of Atomic Energy.

KATHARINE WILLIAMS: *Tr. A. Indust. M. Off.*, 7: 34, 1957.

Nuclear physics was until recently a highly recondite subject confined to a small band of research workers in a few universities. Today the new industry of nuclear energy is a major development, which will bring with it revolutionary changes in technique.

After indicating the development previous to January 1939, and reviewing briefly the nuclear reaction—splitting of the uranium atom—first interpreted in January 1939, the author discusses the impact of this discovery on medicine and on industry. She stresses the fact that the ultimate basis for the exploitation of the uses of properties of radiation is economic.

The isotopes are being used in two main ways: as sources of radiation and as tracers in research. The main impact is felt in the tremendous stimulation to research—the research and development required for the new materials of the atomic age; the research made possible by the use of radioactive tracers; the research into the possibilities afforded by the megacurie sources from the by-products of nuclear energy.

Industrial research laboratories are finding radioactive tracers invaluable in studies of problems such as friction, lubrication, diffusion and a wide range of chemical processes. In this way many industrial problems have been explained. Process control in industry by the use of small sources of radiation is well established. Gamma-active sources are used for radiography.

The use of megacurie sources in sterilization procedures is of considerable interest. It is suggested, however, that this will be adopted only if it proves an economic proposition. The chemical industry also will not discard developed and well-tried chemical processes unless some marked advantage accrues.

It does not appear likely that the uses of radioisotopes in the treatment of disease will significantly alter the present approach; it will consist rather in an extension and refinement of methods in use. As a tool in biological research, radioactive tracers are having the most profound effect. Very important information has been revealed, particularly in tracing the pathways of biosynthesis. Much has been revealed also regarding concepts in plant nutrition and fertilizer practice.

MARGARET H. WILTON

The Control of Industrial Bladder Tumours. A Code of Working Practice Recommended by the British Dyestuffs Industry for the Manufacture and Use of Products Causing Tumours of the Bladder.

T. S. SCOTT AND M. H. C. WILLIAMS: *Brit. J. Indust. Med.*, 14: 150, 1957.

Present-day knowledge in Great Britain regarding the danger of bladder tumours among dyestuffs workers is presented in detail, together with a discussion of the basic principles which must lie behind all efforts to completely eradicate this hazard from the industry. The recommendations derived are made in the belief that if they are implemented, the incidence of bladder tumours in such workers will be reduced to a level no greater than that in the general population. However, with additional knowledge, further amendments and additions may become necessary.

Medical recommendations are discussed with reference to: proper selection and adequate medical supervision of the workers; maintenance of accurate medical and industrial records; early diagnosis, treatment and follow-up of established cases of tumour. Attention is drawn also to plant and operating precautions including design and ventilation of buildings, handling of products, and disposal of residues.

Detailed consideration is given in connection with the manufacture and use of each relevant compound. The associated dangers are indicated and special precautionary measures outlined. Where necessary, explanations based on experience of factory conditions are included, together with any observations resulting from animal experiments. The compounds are considered under the following headings: beta-naphthylamine, Tobias acid (2 naphthylamine-1-sulphonic acid), benzidine, benzidine azo colours, *o*-tolidine, dianisidine, and dichlorbenzidine, alpha-naphthylamine, alpha-naphthylamine sulphate, alpha-naphthol, naphthionic acid, sodium naphthionate, phenyl-alpha-naphthylamine, ethyl-alpha-naphthylamine, rubber chemical manufacture from alpha-naphthylamine, alpha-naphthylamine condensation colours, phenyl-beta-naphthylamine, alpha-naphthylamine azo colours, auramine manufacture, magenta manufacture, and xenylamine (4-aminodiphenyl).

The authors hope that the recommendations in this report will be carried out by the industry as soon as practicable, but they draw attention to the fact that the possible benefits will not necessarily be visible for many years. MARGARET H. WILTON

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OBITUARIES

DR. WILLIAM MACPHERSON CODY, 71, died on April 5 at his home in Hamilton, Ont., where he had lived for 45 years. He was born in Kemptville, Ont. He entered the faculty of medicine of the University of Toronto in 1907, graduating in 1911. He then entered private practice with his father, Dr. W. S. Cody, but in 1919, he gave up general practice to specialize in anæsthesia. Until 1946 he was senior anæsthetist at the Hamilton General and Mount Hamilton Hospitals. He joined the consulting staff at Hamilton General Hospital in 1946.

Dr. Cody is survived by his widow, a son and a daughter.

WALTER REGINALD DICKIE, aged 68, retired Digby (N.S.) physician and surgeon, lost his life as a result of a fire which destroyed his fishing cabin at Sandy Bottom Lake on April 12. Dr. Dickie was born in Stewiacke and was a son of the late Mr. and Mrs. Alfred Dickie. He graduated from Dalhousie School of Medicine in 1914. His first practice was in Barton. In 1927 he moved to Digby, where he took over the practice of Dr. Roberts, and in this town he remained to practise until his retirement in 1950.

Dr. Dickie was always interested in community and school affairs in the town of Digby. He was partly responsible for the establishment of the Digby Regional High School. He was one of the directors of the Digby General Hospital, and for many years was the head of the x-ray department of this hospital. Dr. Dickie was a member of the first Kiwanis Club of Digby and past master of the Masonic Lodge.

He is survived by his two sons, Hugh and Alfred of Digby, and one daughter Phyllis (Mrs. (Dr.) Claude Keays) of Halifax. His wife predeceased him four years ago, as did a son, Dr. Dudley Dickie of Digby.

DR. JOHN A. PETERS, 38, died suddenly in Concordia Hospital, Winnipeg, on April 16. He came from Russia to Canada at ten years of age, graduated in medicine from the University of Manitoba in 1951 and engaged in general practice.

Dr. Peters is survived by his widow, two sons and a daughter.

DR. ARVID CONSTANTIN SILVERBERG of Alderwood Manor, Washington, died on November 13, 1957 as a result of a car accident. He graduated in medicine from McGill University in 1923. He was a general practitioner and was on the staff of the Swedish Hospital, Columbia Hospital and Kings County Hospital.

Dr. Silverberg is survived by his widow.

DR. EDWIN T. TANTON, 76, died at his home on April 13. He was born at St. Eleanor's, P.E.I., and received his medical education at McGill University, where he graduated in 1908. After graduating he began to practise in Summerside, P.E.I., and remained there until the time of his death. Dr. Tanton was also health officer for Summerside. In 1932 he became a Fellow of the American College of Surgeons, and in 1957 he was appointed to represent P.E.I. and Newfoundland as a governor of the College. He was a senior member of the Canadian Medical Association.

Dr. Tanton is survived by his widow and four children, Dr. B. W. Tanton of Vancouver, Dr. T. M. Tanton of Woodstock, N.B., Dr. C. W. Tanton of Montreal and Mrs. F. F. Rutherford of Waterloo.

DR. D. E. S. WISHART, aged 69, died in Toronto on April 8. He was one of Canada's most prominent specialists in deafness and for many years was head of the ear, nose and throat department of the Hospital for Sick Children.

Dr. Wishart was born in Toronto and was educated at the Model School and the University of Toronto. After graduation in arts and medicine, he took extensive postgraduate work in the U.S. and Britain. In 1915 he enlisted and served with the Royal Army Medical Corps, being mentioned in dispatches for service in Salonika in 1917.

In 1922 he joined the staffs of the Hospital for Sick Children and the University of Toronto. The following year, Dr. Wishart became surgeon-in-chief of the hospital's department of otolaryngology. He was elected president of the American Otological Society in 1955.

He is survived by his widow, two sons and one daughter.

FORTHCOMING MEETINGS

CANADA

CANADIAN FEDERATION OF BIOLOGICAL SOCIETIES (Canadian Physiological Society, Pharmacological Society of Canada, Canadian Association of Anatomists, Canadian Biochemical Society), First Annual Meeting, Kingston, Ont. (Dr. E. H. Bensley, Honorary Secretary of the Board, Canadian Federation of Biological Societies, Montreal General Hospital, 1650 Cedar Avenue, Montreal 25, P.Q.) June 7-11, 1958.

CANADIAN OTOLARYNGOLOGICAL SOCIETY (SOCIÉTÉ CANADIENNE D'OTOLARYNGOLOGIE), Annual Meeting, Halifax, N.S. (Dr. Donald M. MacRae, 324 Spring Garden Road, Halifax, N.S.) June 9-11, 1958.

CANADIAN TUBERCULOSIS ASSOCIATION, 58th Annual Meeting, Quebec City, P.Q. (Dr. G. J. Wherrett, Executive Secretary, Canadian Tuberculosis Association, 265 Elgin St., Ottawa 4, Ont.) June 9-12, 1958.

CANADIAN OPHTHALMOLOGICAL SOCIETY (SOCIÉTÉ CANADIENNE D'OPHTALMOLOGIE), 21st Annual Meeting, Halifax, N.S. (Dr. R. G. C. Kelly, Secretary, 90 St. Clair Ave. West, Toronto 7, Ont.) June 12-14, 1958.

CANADIAN ASSOCIATION OF PLASTIC SURGEONS, Annual Meeting, Toronto, Ont. (Dr. D. C. Robertson, Medical Arts Bldg., 170 St. George St., Toronto 5, Ont.) June 12-14, 1958.

CANADIAN NEUROLOGICAL SOCIETY, 10th Annual Meeting, Toronto, Ont. (Dr. J. L. Silversides, Secretary-Treasurer, Suite 321, Toronto Western Hospital, Toronto.) June 12-14, 1958.

THIRD CANADIAN CANCER RESEARCH CONFERENCE, Honey Harbour, Ont. (Dr. Robert L. Noble, Medical Research Laboratory, University of Western Ontario, London, Ont.) June 15-19, 1958.

CANADIAN MEDICAL ASSOCIATION, 91st Annual Meeting, Halifax, Nova Scotia. (Dr. A. D. Kelly, General Secretary, The Canadian Medical Association, 150 St. George Street, Toronto 5, Ont.) June 16-20, 1958.

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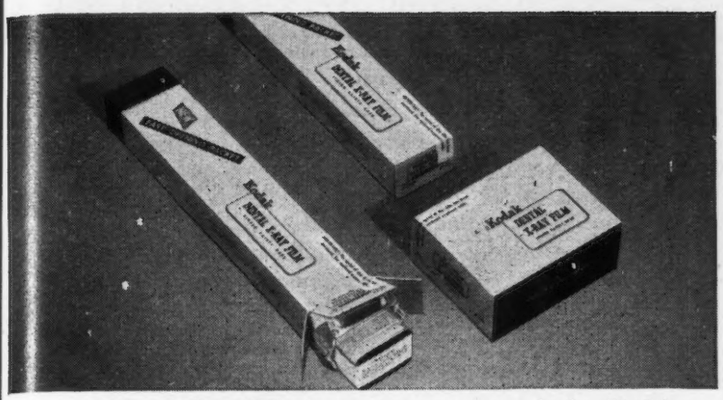
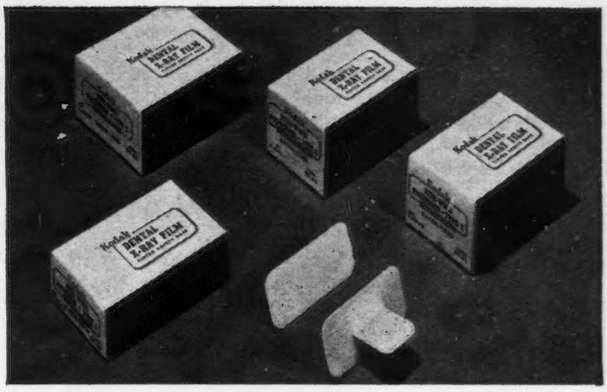


1. **September, 1955:** Announcement was made that Kodak Periapical Ultra-Speed Dental X-ray Film had been made *3 times faster* than the previous film.



2. **September, 1956:** *The doubling of the speed* of Kodak Radia-Tized Films—Periapical and Bite-Wing—was announced.

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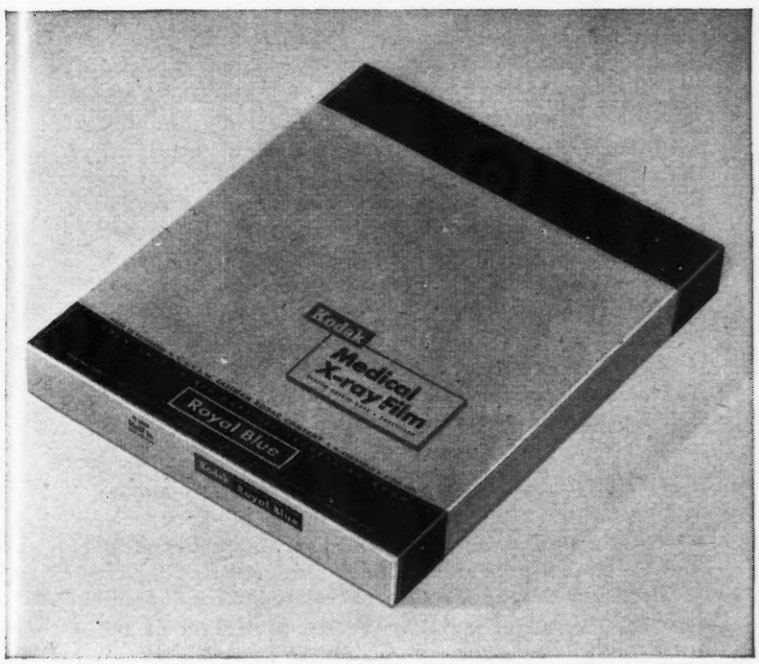
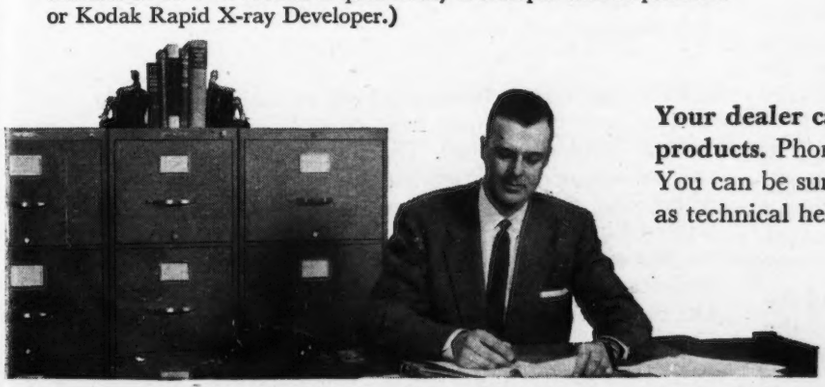


3. **October, 1957:** Kodak Royal Blue Medical X-ray Film—*the fastest medical x-ray film available*—was introduced. (Experience shows that exposures can generally be cut in half—with development for 5 minutes at 68 F in Kodak Liquid X-ray Developer and Replenisher or Kodak Rapid X-ray Developer.)

4. **February, 1958:** New Kodak No-Screen Medical X-ray Film now available. *Increases speed 50%.*

5. **February, 1958:** Kodak Photoflure Medical X-ray Film, Green Sensitive, 35mm and 70mm rolls, *now twice as fast.*



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CANADIAN RHEUMATISM ASSOCIATION (SOCIÉTÉ CANADIENNE DE RHUMATOLOGIE), Annual Meeting, Vancouver, B.C. (Dr. de Guise Vaillancourt, Secretary, Canadian Rheumatism Association, Hôtel-Dieu Hospital, Montreal 18, Que.) June 18, 1958.

CANADIAN DERMATOLOGICAL ASSOCIATION, Annual Meeting, Halifax, N.S. (Dr. Gibson E. Craig, Secretary, Suite 6, 1390 Sherbrooke St. West, Montreal 25, Que.) June 19-21, 1958.

CANADIAN PSYCHIATRIC ASSOCIATION, Annual Meeting, Halifax, Nova Scotia. (Dr. Charles Roberts, P.O. Box 6034, Montreal, Que.) June 20-21, 1958.

INTERNATIONAL FERTILITY ASSOCIATION, Windsor Hotel, Montreal, Que. (Dr. Walter W. Williams, 20 Magnolia Terrace, Springfield 8, Mass., U.S.A.) June 20-22, 1958.

INTERNATIONAL FEDERATION OF GYNÆCOLOGY AND OBSTETRICS, 2nd Congress, Montreal, P.Q. (Professor Léon Gérin-Lajoie, Suite 313, 1414 Drummond Street, Montreal, P.Q.) June 22-28, 1958.

10TH INTERNATIONAL CONGRESS OF GENETICS, Montreal, P.Q. (Mr. J. W. Boyes, General Secretary, 10th International Congress of Genetics, McGill University, Montreal, P.Q.) August 20-27, 1958.

UNITED STATES

AMERICAN GOITER ASSOCIATION, Annual Meeting, San Francisco, Cal. (Dr. John C. McClintock, Secretary, 149½ Washington Ave., Albany 10, New York.) June 17-19, 1958.

AMERICAN COLLEGE OF CHEST PHYSICIANS, 24th Annual Meeting, San Francisco, Cal. (Mr. Murray Kornfeld, Executive Director, 112 East Chestnut St., Chicago 11, Ill.) June 18-22, 1958.

AMERICAN MEDICAL ASSOCIATION, Annual Meeting, San Francisco, California. (Dr. George Lull, 535 North Dearborn Street, Chicago 10, Ill.) June 23-27, 1958.

PROVINCIAL NEWS

MANITOBA

Winnipeg played host to two national groups on April 14, 15 and 16. The College of General Practice held its second annual meeting in the Royal Alexandra Hotel. Over 600 registered from across Canada, and the proceedings were well covered in the local press. Members of the Canadian Gynæcological Travel Society were the guests of Dr. Elinor Black, Department of Obstetrics and Gynæcology, Faculty of Medicine, University of Manitoba, and the Winnipeg General Hospital. Members of the local department presented the program. Dr. Lennox G. Bell, Dean of the Faculty of Medicine, was the guest speaker at the annual banquet.

Dr. Irwin J. Schatz has been appointed a Fellow in medicine in the Mayo Foundation at Rochester, Minn., a part of the Graduate School of the University of Manitoba Medical School.

Dr. William A. Lange, of Detroit, who addressed the Canadian College of General Practice, spoke to the Winnipeg Medical Society on April 16 on "Surgical Correction of Congenital Abnormalities". Professor C. C. Ferguson led the discussion.

The first automatic x-ray film-processing unit in Canada has been installed in Winnipeg General Hospital at a cost of $30,000. It produces a finished readable print in six minutes and eliminates the human element of error in handling. Two hundred and forty of the largest x-ray films may be processed in an hour.

The annual report of the Manitoba Cancer Relief and Research Institute shows that in 1956 a total of 2248 new cancer cases, including second primaries, was reported. Of these 75% were followed through the tumour service. The clinical research group includes Dr. H. Blondal, Dr. J. H. Linford, Dr. L. G. Israels and Dr. J. P. Maclean. The main lines of interest are the chemotherapy of leukæmia, the effect of polysaccharides on malignant effusions in humans, the biological effects of ionizing radiations, and hormonal factors in carcinoma of the breast. ROSS MITCHELL

ONTARIO

Dr. A. B. Whytock, Niagara Falls, has been elected president of the College of Physicians and Surgeons of Ontario. The vice-president is Dr. J. J. Day, Ottawa. Committees appointed were: *Executive*: Dr. A. B. Whytock, Dr. J. J. Day, Dr. G. E. Hobbs, London; Dr. R. M. Mitchell, Sudbury; Dr. D. S. Wigle, Windsor. *Discipline*: Dr. E. M. Mitchell, Sudbury, chairman; Dr. J. S. Delahaye, Kingston; Dr. S. J. Forrest, Toronto; Dr. W. C. Givens, Toronto; Dr. E. R. S. Wyatt, Elmira. *Education and Registration*: Dr. G. E. Hobbs, London, chairman; Dr. Malcolm Brown, Kingston; Dr. J. A. Dauphinee, Toronto; Dr. J. S. Delahaye and Dr. F. L. Rose, London. *Legislation*: Dr. J. A. Dauphinee, chairman; Dr. J. A. Hannah, Toronto; Dr. F. L. Rose, Dr. J. W. R. Webster, Ottawa; Dr. D. S. Wigle. *Finance, Printing and Property*: Dr. J. A. Hannah, chairman; Dr. C. E. Bond, Toronto; Dr. S. J. Forrest, Dr. J. W. R. Webster, Dr. E. R. S. Wyatt.

Dr. C. H. Best recently received an honorary doctorate from the Central University of Venezuela, where he lectured on "Contributions of the biological sciences to public health in the future". Other subjects he discussed during his visit there were "Insulin and diabetes", "Choline and the dietary protection of the liver" and "Thrombosis and heparin".

He was given the freedom of the City of Caracas, honorary life membership in the Venezuelan Endocrine Society and in the Venezuelan Antidiabetic Association, and a membership in the Venezuelan Society for the Advancement of Science.

Five travelling orthopædic Fellows, one from South Africa and the others from the United Kingdom, visited Toronto in April. The object of these tours is the exchange of information among English-speaking orthopædic surgeons. One year the Fellows come from United Kingdom and one other Commonwealth country to this side of the Atlantic, and the following year American and Canadian Fellows visit Great Britain. Dr. R. I. Harris was instrumental in initiating this idea

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eight years ago. The Fellows spend a month in travel and study. Expenses are met by the British, American and Canadian Orthopædic Associations.

Among the papers they heard in Toronto were: "The experimental use of dermis in arthroplasties"—Dr. E. Simmons and Dr. J. Murray; "Arthrography in lesions of the shoulder joint"—Dr. James Bateman; "Osteoporosis"—Dr. Glen MacDonald; "Lesions of the interarticular disc of the wrist joint"—Dr. H. Coleman; "Use of and advances in prostheses"—Dr. W. R. Harris; and "Fracture dislocation of the pelvis"—Dr. G. Pennal.

Mr. Edson L. Haines, Q.C., Toronto, addressed the Essex County Medico-Legal Society in April on "Courts and doctors".

Dr. J. H. Maus, Windsor, has been elected to membership in the American Radium Society; earlier this year he became a member of the American College of Radiology.

The pharmacists of Windsor have organized Prescription Services Incorporated to enable the public to prepay the cost of drugs. The policies are to be taken out on a group basis until the number insured reaches 3000 when a survey will be made. No more groups will be accepted until the survey is completed; this will take from 12 to 18 months.

The Physiological Society of the University of Toronto was addressed by Dr. Murray Saffan, Allen Memorial Institute of Psychiatry, McGill University, on "Studies on pituitary corticotropin" and by Dr. V. W. Adamkiewicz, Department of Physiology, University of Montreal, on "Insulin and the dextran 'anaphylactoid' inflammation". LILLIAN A. CHASE

The Section of Cardiology of the Ontario Medical Association held its combined annual meeting with the Western New York Heart Association in Rochester, N.Y., on April 10, 1958. There were over 150 registrants at the Rochester Academy of Medicine, a beautiful building situated in ideal surroundings to the east of the city. Participants were welcomed by Dr. Arthur Walker, President of the Medical Society of the County of Monroe, and Dr. N. L. Kaltreider, President of the Rochester Academy of Medicine. The morning session included papers on the use of homologous trachea as aortic grafts by Kopf and Wiles of Buffalo, the effect of mitral commissurotomy on the clinical course of mitral stenosis by Aldridge and his colleagues of Toronto, hypothermia and coronary perfusion of intracardiac surgery by Mahoney and his colleagues of Rochester, the use of chlorothiazide by Doyle of Buffalo, and pulmonary circulatory dynamics and right ventricular function in mitral stenosis during exercise by Stanfield of Rochester.

The afternoon session was chaired by Dr. Donald B. Moran of Toronto and included papers on the value of the standard clotting time test for control of oral anticoagulant therapy by Mayer of Kingston, congenital bicuspid aortic valves in relationship to aortic stenosis by Matthews of Buffalo (a most entertaining paper), and corneal arcus, coronary atherosclerosis and serum lipids by Shanoff of Toronto. The session closed with a panel discussion of various cases, in which the moderator was Dr. D. P. Murnagham of Toronto and the other participants were Drs. Gunton of Toronto, Voltz of Buffalo and Wedd of Rochester.

The Ontario Association of Medical Clinics held their annual meeting at Orillia on Saturday, May 3, 1958. The program included a discussion of clinic costs by C. S. Redden, Administrator, The Peterborough Clinic, Peterborough; "Some Facets of the Hospitalization Plan", by R. W. T. Urquhart, M.A., M.D., Ontario Hospital Services Commission; and "Scientific Meetings on Clinics", by A. F. Perl, M.D., Carruthers Clinic, Sarnia.

Officers for the coming year are: President: Dr. R. K. Magee, The Peterborough Clinic, Peterborough, Ont. Vice-President: Dr. A. F. Perl, Carruthers Clinic, Sarnia, Ont. Past-President: Dr. B. H. Handy, Rynard Clinic, Orillia, Ontario. Secretary-Treasurer: Mr. C. S. Redden, The Peterborough Clinic, Peterborough, Ontario. Directors: Dr. Wm. Bryant, Kirkland Lake Medical Group; Dr. C. Pinch, Guelph Medical Group, Guelph; Dr. O. G. Mills, Oshawa Clinic; Dr. A. C. Johnson, McGregor Clinic, Hamilton.

The Ontario Hospital Services Commission has produced a 25-minute film (16 mm. black and white) entitled "Hospital Insurance in Ontario", to explain the details of the plan for hospital insurance which will begin operation in the province on January 1, 1959. The film is available on free loan to church groups, farm groups, service clubs, and business and professional groups, and can be obtained by writing to the Ontario Hospital Service Commission, Parliament Buildings, Queen's Park, Toronto 5.

QUEBEC

Under the ægis of the Department of Psychiatry of McGill University and the Department of Psychiatry of Queen Mary Veterans Hospital, a three-day conference on psychodynamic, psychoanalytic and sociological aspects of the neurolytic (tranquillizing) drugs in psychiatry was held at the latter hospital, April 11 to 13. Many prominent psychiatrists from Canada as well as the United States participated. Five working committees spent part of the first two days in detail studies along specified lines. In addition there were general sessions. The last day was devoted to open discussions of reports presented by the committee chairmen. It was not all work, however, and among social functions was a reception (vin d'honneur) by His Worship the Mayor of Montreal. It is hoped that the proceedings and resulting committee reports will soon be available in monograph form. [An account of the proceedings appear on p. 797 of our May 15 issue.—ED.]

The 37th annual banquet of the Osler Society of McGill University was held on March 27. The guest speaker was Dr. William C. Gibson, Kinsman Professor of Neurological Research of the University of British Columbia. Professor Gibson has been elected Life President of his Class of McGill of '41; as a student he was president of the Osler Society. Since graduation he has continued with his student en-

thusiasm in Osleriana and in the history of medicine. He spoke on "Scientific Discoveries by Medical Students". The expanded version of this is to appear soon in book form.

In the Montreal area several campaigns for financial aid to hospitals and for additional hospital construction are in progress. A grand ball followed the opening ceremonies of our new Queen Elizabeth Hotel on April 16. The entire proceeds from this affair, at $100 a couple for some 500 couples, went to the Montreal Children's Hospital and St. Justine Hospital. All expenses of the ball including the banquet, refreshments, tips and entertainment were covered by the Queen Elizabeth.

Early in June, a six-storey addition to Queen Elizabeth Hospital will be started. This will be the first major building project since the hospital was built in 1927. It is hoped that this will accommodate another 5000 patients yearly. It will also provide more out-patient accommodation and give additional facilities for obstetrics, radiology and physiotherapy.

The Jewish General Hospital has just completed a successful campaign for $3,000,000 for expansion. This will permit radical and extensive alterations to rooms and wards in the original building, as well as provision of 125 beds by the addition of two floors to the recently completed west wing and two floors to the north wing of the main building. Apart from patient care, the hospital plans to increase its scientific research facilities and intensify its postgraduate medical education program. In addition, provision is being made for a psychiatric in-patient department to add to the facilities of present out-patient services in this field.

Premier Maurice Duplessis has announced that the first diagnostic centre for the province will soon be established in Montreal, in the old St. Justine Hospital building on St. Denis Street, which was bought some time ago by the provincial government. Fairly extensive and costly alterations to the present building are planned. The only other information so far obtainable is that the facilities will be available to all practising physicians.

During the past six months Dr. Ruth McDougall has made a careful study of traffic accident admissions to the Montreal General and the Montreal Children's Hospitals. One purpose of this study was to establish clues on how researches should proceed in a larger study, such as might be undertaken by the newly chartered Canadian Medical Traffic Accident Research Foundation. Dr. McDougall presented her findings to the staffs of the two hospitals on April 18. About 80% of the patients were treated in the emergency out-patient department and only 20% were admitted to hospital. For those admitted, the average stay was about 25 days, ranging from one day to 145 days. Most casualties came from within a radius of two miles of the hospital and only 16% came from outside the City of Montreal proper. More than a quarter of all accidents studied occurred between midnight and 4 a.m., when traffic is light. About 22% occurred between 4 and 6 p.m., when traffic is heavy. At the Children's Hospital only about 30 patients treated were victims of traffic accidents, compared with 300 victims of accidents not involving vehicles, mainly in the home.

Dr. McDougall found that the hardest factor to establish was the cause of the traffic accident. The best source is usually the victim. Her presentation definitely indicated that an extended study would be better if special investigators were used to ferret out data.

The greatest needs of our senior population today include periodic revision of old age pensions, appropriate housing and better recreation facilities. This was the consensus of opinion of the panel who discussed geriatrics before a group of close to 100 nurses at Queen Mary Veterans Hospital on March 20. The chairman of the panel was Dr. Paul G. Weil and the members were Drs. Angus Bowes and W. F. T. Tatlow, Miss Jeannine Buteau, medical social worker, and Miss M. A. Gage, assistant district director, Victorian Order of Nurses. The most important aspect as regards medicine is the necessity to get old people to look after themselves. People develop talents in a lifetime and they must be encouraged to use them in old age. Otherwise they lapse into lethargy and complications develop. However, not only must the patient be taught to care for himself, but the family also must be educated to the needs and capabilities of the elderly patient.

Dr. Louis M. Lehoux, who has been a Fellow in otorhinolaryngology at the Mayo Foundation in Rochester, Minn., since 1954, has recently established a specialist practice in Quebec City.

Dr. Robert F. Ingram has been appointed as executive director of the Montreal Children's Hospital. He will assume these new duties on June 1 and succeeds Dr. John E. de Belle, who is retiring for reasons of health. Dr. de Belle will continue to act as consultant administrator to the hospital. Dr. Ingram, at present assistant to the executive director of the Royal Victoria Hospital, is a graduate of Dalhousie University and the University of Toronto. After serving in the R.C.A.M.C., he practised medicine in Bathust, N.B., before joining the administrative staff of the R.V.H.

Dr. Donald C. Bews of Montreal, medical director of the Bell Telephone Co., was elected a director of the Industrial Medical Association at its 43rd annual meeting in Atlantic City, N.J. Dr. Bews, who will serve for a three-year term, is now the only Canadian member of the board of directors. A. H. NEUFELD

NOVA SCOTIA

Dr. John Stallworthy, gynæcologist-in-chief of the Oxford Regional Group of Hospitals, England, arrived in Halifax on Good Friday en route to the West for lecture engagements in Canada and the U.S.A.

Members of the Department of Obstetrics and Gynæcology, Dalhousie University, spent two very fruitful sessions with him, exchanging ideas concerning the specialty. All agreed that this was a stimulating visit. He and his wife also had an opportunity of seeing some of the scenic beauty along the South Shore of Nova Scotia.

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Entrance scholarships into the Faculty of Medicine of Dalhousie University have been awarded to John F. Hamm, James G. Holland, David C. Murray, Marven L. Brook, Morton L. Brown and David W. J. Gough.

Two scholarships of $500 are awarded to residents of the mainland of Nova Scotia. One of these has been awarded to John F. Hamm, New Glasgow, of King's College University in Halifax. Mr. Hamm has attained an excellent academic record and was granted the B.Sc. degree in May. The second scholarship for Nova Scotia has been divided between two students of high standing: James G. Holland of Halifax, and David C. Murray, of Springhill. Mr. Holland received his early education at Queen Elizabeth High School in Halifax, and at Dalhousie University, where he received an honours B.Sc. degree in May. He has already had an entrance scholarship to Dalhousie and at the end of his first year he was awarded the George H. Campbell Memorial Scholarship. Mr. Murray has attained high scholastic standing in his three years of pre-medical studies at St. Francis Xavier University.

One scholarship, awarded to a resident of Cape Breton Island, goes to Mervin I. Brook of Sydney. He obtained his early education at Sydney Academy, going to Dalhousie University on an entrance scholarship in 1956. He was also awarded a University scholarship in 1957.

On April 16, the community of Bass River gathered at the Community Hall to welcome Dr. and Mrs. J. Wilson and family to Bass River. Rev. W. K. MacKay gave the address of welcome to the new family. Dr. Wilson expressed his thanks for the welcome they had received.

Dr. Lloyd B. MacPherson, M.B.E., has been appointed Assistant Dean of Medicine at Dalhousie University. This newly created position was announced by President A. E. Kerr and was the recommendation of medical educators, representing both Canadian and American medical colleges and the two national medical associations.

This group of medical educators made favourable comments on the "high morale and dedication to teaching and research and the unique loyalty to the institution, and said that it should be a matter of great pride to the Faculty of Medicine, the University and the Atlantic Provinces". This committee emphasized that the complexity of a modern medical centre imposes diverse and heavy responsibilities upon the Dean, and they recommended that an assistant be appointed to Dean C. B. Stewart to relieve him of part of the burden of his administrative duties.

The first assistant dean, Dr. Lloyd B. MacPherson, has been a member of the Department of Biochemistry of Dalhousie University since 1952, with the present rank of Associate Professor. He will continue his research and teaching in that department as well as serving on a part-time basis as assistant dean.

Dr. MacPherson obtained his B.Sc. at Acadia University and proceeded to graduate study in biochemistry in the Department of Medical Research at the University of Toronto, where he was associated with the late Sir Frederick Banting. During World War II he spent six years in the Canadian Army overseas in command of the Canadian Chemical Warfare Laboratory. He was appointed a member of the Order of the British Empire in 1944 in recognition of outstanding services. After the war he completed his training in the University of Toronto and was awarded the degree of Ph.D. in Pathological Chemistry in 1948.

NEWFOUNDLAND

The provincial government announced in February and March a program of enormous capital expenditure in the fields of health, education, road-building, and rural electrification. The means of financing these projects, estimated to cost over $100,000,000, has been the subject of comment during the recent political campaign, and the budget is awaited with interest.

It is envisaged that about $20,000,000 will be spent in improvements in the sphere of public health over a period of five years, beginning with an expenditure of about $2,500,000 in the new fiscal year. Most of this will be used to build new hospitals and to add to existing ones. Special attention has been given to increasing facilities for the care of children, which have, up to the present, been very deficient; this is in accordance with recommendations made by a special committee of the Newfoundland Medical Association. The total number of new beds for children will be 370. The additional annual cost of maintenance of these new facilities is estimated to be about $5,000,000.

The projected hospital improvements are as follows:

New hospitals.—Grand Falls (125 beds), Gander (110 beds), Bell Island (75 beds), Clarenville (75 beds), Baie Verte area (30 beds).

Additions to existing hospitals.—General Hospitals, St. John's (200 beds), Mental Hospital, St. John's (500 beds), Corner Brook (115 beds).

Improvements to existing cottage hospitals.—Old Perlican, Placentia, Fogo, Brookfield, Bonne Bay, Stephenville Crossing, Burin.

In addition to this hospital construction, a $3,000,000 nurses' residence will be erected in St. John's, alterations will be made to the regional laboratory on the west coast, and there will be new or improved physicians' residences at Brookfield, Hermitage, St. Joseph's (St. Mary's Bay), Stephenville Crossing, Burin and St. George's. Additional physicians will be obtained for Jeffrey's, St. Lawrence, Port Saunders, Old Perlican, Hampden, Stephenville Crossing and Brookfield.

This prodigious plan would make a substantial contribution toward remedying present inadequacies. Newfoundland's health needs have been intensively studied in the past couple of years in preparing this province's case for presentation to the Royal Commission appointed under the terms of Confederation to study our financial situation. This study showed that this province would need, by 1963, a total of 3000 general hospital beds and about 1600 mental hospital beds. If the present plan is carried through, there will still be a deficiency of about 600 general and about 600 psychiatric beds to bring such accommodation in this province up to generally accepted standards.

Grand Falls Hospital

Before the above program of hospital construction was announced, much preliminary work had already

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been done in Grand Falls towards a new, larger hospital. Since the summer of 1957 a citizen's committee has been hard at work, with the advice and active support of Dr. William Janes. The population of the Grand Falls area, which includes Bishop's Falls and Windsor, has grown to over 15,000; the need for extension of the present facilities (30 beds) has been apparent for some time. It now appears that building will be under way within a year or so.

The committee have had discussions with the provincial department of health and with the Anglo-Newfoundland Development Company, and have visited Corner Brook to study the methods of financing and operation of the Western Memorial Hospital. The A.N.D. Company, the chief industrial organization in the region, has brought in a team of experts from the mainland to prepare a survey and to advise concerning local methods of raising the necessary money.

It is intended to put up a 125-bed hospital, containing 50 beds for children. The cost of this will be around $2,000,000, of which $350,000 must be obtained locally, the remainder to come from the provincial and federal governments. ANGUS J. NEARY

BOOK REVIEWS

A SHORT HISTORY OF ANATOMY AND PHYSIOLOGY FROM THE GREEKS TO HARVEY. (The Evolution of Anatomy.) Charles Singer. 209 pp. Illust. Dover Publications, Inc., New York; McClelland & Stewart Limited, Toronto, 1957. $1.95.

In 1925, Dr. Singer produced a most readable book on the history of anatomy, founded on the Fitzpatrick lectures given by him at the Royal College of Physicians. This unique contribution to medical history, *The Evolution of Anatomy*, has long been out of print. It is now reissued as a "paperback" by Dover Publications, with a new name and some minor corrections. Copiously illustrated, it tells the story of anatomy from earliest times to the age of Harvey, and has as a supplement a number of plates by Vesalius, an anatomist to whom, as the most influential figure of his period, Singer devotes much space. Galen is also dealt with in suitable detail after a rapid survey of the pre-Galenic anatomists. Much of the book naturally follows the fortunes of the Bologna and Padua schools in their periods of fame.

At the modest price asked for this book, there is no excuse for any student of anatomy or medical history to neglect this little classic, and incidentally combine instruction with entertainment.

CLINICAL PATHOLOGY DATA. Compiled by C. J. Dickinson, Medical Registrar, Middlesex Hospital. 91 pp. 2nd ed. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $4.75.

This small volume of 91 pages contains a large amount of useful factual data pertaining chiefly to tests performed in the clinical pathological laboratory. The purpose of the book is to have readily available tables showing the normal values of the different constituents of blood, urine and spinal fluid, as well as the normal values for many laboratory tests. Of considerable use in the tables given are the lists of conditions wherein abnormal results are found in these procedures. The results of many tests for endocrine function are also presented, as well as those related to immunology.

A small section devoted to unnecessary "tests" is one of the features of this little volume. The index includes both diseases and tests appropriate to such diseases, the more important ones being in bold-face type.

For the busy practitioner this small volume should be of considerable help in allowing him to decide which tests to order and the significance of the results.

THE CLINICAL APPLICATION OF ANTIBIOTICS. Volume III: Chloramphenicol and the Tetracyclines. M. E. Florey. 393 pp. Oxford University Press, London, New York and Toronto, 1957. $9.75.

Professor Florey has brought his readers up to date in the antibiotic field in the third volume of his series. Although this book went to print in 1956, the information it contains is applicable to present-day therapy, apart from the remarks on staphylococcal infections. With regard to this organism, therapy changes so frequently that the reader is advised to consult a journal published weekly.

This book is more than the title would indicate, in that there is a precise description of each drug, including its origin, chemistry and bacteriological effects. Each of the antibiotics is discussed separately, with full explanation of indications for treatment, side-effects and toxicity. The chapters in general considerations are beautifully concise and descriptive, and any clinician would be well advised to read them.

This book gives one a thorough knowledge of the subject. The tabulated index makes it useful as a reference book.

CLINICAL AND IMMUNOLOGICAL ASPECTS OF FUNGOUS DISEASES. J. Walter Wilson, University of Southern California, Los Angeles, California. 280 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $7.50.

More than three-quarters of this monograph is given to the study of the fungous lesions known as "deep", and the remainder is concerned with the superficial or skin form of these infections. This allocation is in keeping with morbidity and mortality rates but it is not in proportion to the incidence, for some forms of skin fungus are practically ubiquitous.

The incidence of "deep" fungous lesions is increasing, and the general practitioner must keep these diseases in mind when he is confronted with unusual or inexplicable symptoms. When skin signs are also present the dermatologist can help, but in the absence of such signs recourse must be had to the mycological laboratory.

The chief merit of this monograph is the account it gives of the methods used by the laboratory worker in the search for the causative organism. The presentation of these methods in a succinct and easily readable form is not a simple matter, but in this work the author has managed to make the presentation of a comfortable brevity without sacrificing clarity.

Illustrations would help to keep the reader's interest, but probably they could not be had within the price range of these monographs.

LEHRBUCH DER ROENTGENOLOGISCHEN DIFFERENTIALDIAGNOSTIK: Band I, Erkrankungen der Brustorgane (Textbook of Roentgenological Differential Diagnosis: Vol. I, Diseases of the Chest). 1183 pp. Illust. 4th ed. Werner Teschendorf, Köln. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1958.

Professor Teschendorf dedicates this volume on roentgenological differential diagnosis of diseases of the chest to the memory of his late teacher, Prof. Max Matthes, whose *Differential Diagnosis in Internal Medicine* has become one of the classics in medical literature. The pupil has aptly followed *in magistri verba*, as a result of which the *Roentgenological Differential Diagnosis* appears in its greatly enlarged fourth edition.

The text is divided into five major parts. The first and largest deals with diseases of the lungs, pleura and mediastinum, with special emphasis on the segmental anatomy of the lungs. The techniques of bronchography and the method of selective pulmonary angiography as an adjunct to segmental bronchography are discussed in detail. The acquired and congenital diseases of the heart are the subject of a 400-page section by Dr. Thurn. In it, all methods of heart investigation are reviewed, including roentgenkymography and electrokymography, cardiac catheterization, angiocardiography and retrograde aortography and cinéradiography. The heart and the great vessels in their relation to the thoracic cage, the methods of heart measurements, the significance of extracardiac factors in the position of the heart, its configuration, size, the anomalies of the great vessels, the diseases of the coronary arteries, cor pulmonale, the problem of injury to the heart, tumours of the heart and other organs are all subjects of roentgenological differential diagnostic considerations. A special chapter is devoted to the diseases of the œsophagus. The radiologically discernible changes and abnormalities in the diaphragm are also discussed in this interesting book.

The textbook is magnificently illustrated. Its graphic qualities are of the highest order. Its layout is such as to facilitate a quick assessment of the subject under discussion on a given page. On the outer side of each page a half inch of space is left for a brief "headline" of the subject under discussion, e.g. pneumonia, tuberculosis in children, position of the diaphragm in pleural effusion. A welcome change from the usual is the placing of the references at the bottom of each page. Incidentally, the references are brought up to 1957. A complete index is at the end of the textbook.

This book was written with emphasis on standard diagnostic procedures, but all other involved and more complicated methods of roentgenological investigation are thoroughly discussed.

The abundant illustrations have been made with the thought that they will speak to the reader directly and help him with differential diagnostic problems. This purpose has been fully achieved by the authors.

GERMAN-ENGLISH GLOSSARY OF NEUROPHYSIOLOGY. Edited by Roger Merritt Morrell. 181 pp. Consultants Bureau, Inc., New York, 1958. $7.50.

The compiler of this glossary points out that English translations of the voluminous German literature on neurophysiology are rare. He has compiled this list of words as a help to would-be translators. The list contains not only words in neurophysiology but many others in anatomy, biochemistry, physiology, neurology, electrical engineering and electronics, and also a great number of idioms and general words met with in the literature. Dr. Morrell disarms criticism by pointing out that this is only a preliminary work and inviting comment on it. The list will certainly be most useful, but it is regrettable that more care in proofreading was not taken, for there are a number of irritating typographical errors which may baffle the beginner. However, the research worker in neurophysiology will find much material in these pages that he would not readily obtain from ordinary dictionaries.

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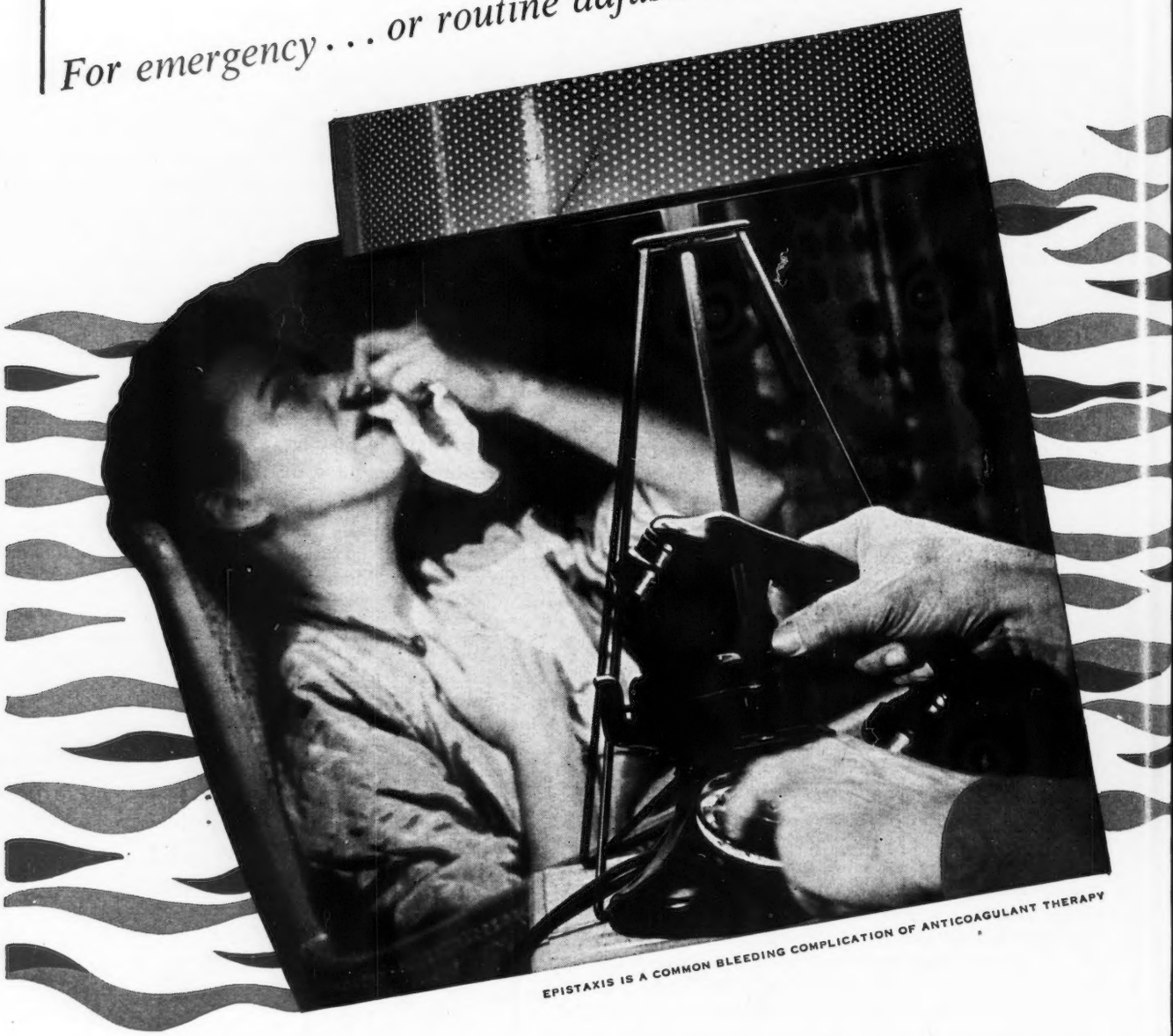

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1. Tulloch, J. and Wright, I. S., *Circulation* 9:823, June 1954.

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*DEVLIN, L.P.: Industrial Medicine and Surgery., 23:4, (1954)

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MEDICAL NEWS *in brief*

(Continued from page 870)

TOPICAL FLUORIDE

Although water fluoridation is the best known method of preventing dental caries on a public health basis, the measure is not available to many segments of the population, particularly those in rural areas with well water supplies. At the fortieth anniversary celebration of the Eastman Dental Dispensary, Rochester, N.Y., a panel discussed the alternative of using topical fluoride preparations on the teeth. One participant suggested that topical fluoride application be made available to all school children not covered by water fluoridation through organized community programs. Another considered that topical fluoride treatment is the practising dentist's best weapon against dental decay. He felt that such applications should be part of each child's recall and prophylaxis visits, so that the teeth receive an application of fluoride at least every six months. Another participant reported results with a topical fluoride cream application; patients who had the cream applied to sound teeth on one side of the mouth developed 43% fewer new cavities in these teeth than in untreated teeth on the opposite side of the mouth.

RECENT ADVANCES IN BRONCHOGRAPHY

Recent advances in bronchography have occurred as a result of new bronchographic media and technique (Rayl and Smith, *Dis. Chest*, 33: 235, 1958). These advances have improved the quality of bronchography to such an extent that small bronchial lesions are more readily seen. A method of correlating these bronchographic defects with their histological appearance has increased our knowledge of the significance of these defects.

Since all bronchographic media remaining in the alveoli may produce foreign body reaction, it is recommended that a technique of bronchography and a type of bronchographic medium be used in which alveolar filling is not seen. There is less alveolar retention after Visciodol than after other bronchographic media.

The technique of selective bronchography with Metras catheters is of value when there is insufficient outlining of a particular segment during a previous bronchographic examination. Routine bronchography in selected cases with an appropriate Metras catheter avoids the necessity of repeated bronchograms.

A roentgenogram made 24 hours after bronchography should become a part of the routine bronchographic procedure so that our attention can be directed to less obviously involved areas of bronchial disease. Roentgenologists should be encouraged to include this in the total cost of the bronchogram.

Newer techniques in bronchography have made possible a more detailed study of bronchial defects. In order to give proper treatment to patients with acute or chronic bronchitis, the authors feel that the less obvious lesions must be recognized on bronchography.

RELIABILITY OF ELECTROCARDIOGRAPHIC DIAGNOSIS OF LEFT VENTRICLE HYPERTROPHY

In a series of 550 unselected electrocardiograms taken on patients in whom necropsy findings were later available, 108 tracings showed the pattern of left ventricular hypertrophy according to currently accepted electrocardiographic criteria. The analysis of the necropsy findings based on heart weights revealed that left ventricular hypertrophy was believed to be present in 75 cases, absent in 17 cases, and questionable in 16 cases. In none of the 17 cases with normal cardiac weight was there known cause for cardiac hypertrophy, nor was significant cardiac disease present. The majority of patients in this group died of malignant disease and showed considerable emaciation. The value of the three principal classes of electrocardiographic criteria was examined not only in the light of confirmed and false-positive cases, but also in cases with mild, moderate, and severe left ventricular hypertrophy determined by cardiac weight. The prolonged ventricular activation time was found to be the least reliable sign, having been present in many false-positive cases and absent in some cases with severe hypertrophy. Increased voltage of precordial leads, the most sensitive of the criteria, was present in most cases. It was also, however, most frequently responsible for a false-positive diagnosis of left ventricular hypertrophy. The depression of S-T segments, flattening and inversion of T waves in leads showing the highest electro-positive deflections when added to the other two groups of criteria materially increased the specificity of the diagnosis. However, the relationship between the extent of the electrocardiographic abnormalities and the severity of hypertrophy is only fair. These inaccuracies in ECG diagnosis are inherent in the method and demonstrate that conventional electrocardiography registers in a rather crude way the electric forces of cardiac action, being influenced by such extraneous factors as body build, vagaries of anatomic position of the heart, the degree of insulating effect of outside structures, and probably other factors, as yet unknown. Currently available ECG criteria for diagnosis of left ventricular hypertrophy appear moderately satisfactory. They should be applied, however, with the understanding of their limitation and accepted as an expression of probability rather than a diagnosis of left ventricular hypertrophy. The disappointing inaccuracy of electrocardiography in diagnosis of early left ventricular hypertrophy is emphasized. – A. Selzer *et al.*: *Circulation*, 17: 255, 1958.

A TUMOUR-PRODUCING AGENT WITH VIRUS CHARACTERS

At a meeting of the American Association for Cancer Research in Philadelphia on April 13, Eddy and Stewart of the National Institutes of Health at Bethesda, Maryland, reported that the cancer-

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producing agent they discovered two years ago has biological and physical properties of viruses. The agent produces multiple tumours in mice and hamsters.

Like viruses, the agent will grow in tissue culture and can be transferred in series from one tissue culture to another without loss of potency. In the present studies, the agent produced tumours in hamsters and mice after being passed through tissue culture many times. The tumour-producing activity of the agent was increased by alternate passage through tissue culture and mice or hamsters.

The agent has other virus characteristics. It is destroyed by heat but not by storage at freezing temperatures. The size of the agent is in the virus range, as indicated by the pore size of the filter through which it passes. The agent is not destroyed by antibiotics, and produces neutralizing antibodies in rabbits.

The tumour-inducing ability of the agent was accelerated when the animals were inoculated with a concentrate of the tissue culture fluid or with the active principle partially purified by chemical procedures. These results indicate that the tumour-inducing agent was concentrated by these methods and that its activity is related to the size of the dose.

This collaborative study originated in observations by Stewart that injection of newborn mice with cell-free mouse leukæmia extracts produced an unusual type of tumour of the parotid (salivary) gland rarely occurring spontaneously in mice. Injection of newborn mice with cell-free extracts prepared from the parotid gland tumours did not produce tumours. But when cell suspensions of parotid gland tumour tissue were maintained in tissue culture and the cell-free supernatant fluids injected into newborn mice, the mice developed tumours. All mice that developed such tumours had primary parotid gland tumours, and some also developed tumours of the thymus, adrenal glands, and mammary glands. Similar results were obtained when an extract from a spontaneous mouse leukæmia was used.

These results suggested that a subcellular tumour-inducing substance multiplies and acquires increased activity in tissue culture.

WHY DOES TUBERCULOSIS REACTIVATE?

Reactivation of tuberculosis is due to the presence of virulent viable tubercle bacilli that remain in the tissues. Because of the tendency of blood vessels in the involved area to be obliterated, antimicrobial therapy does not penetrate into the caseous areas and thick cavitary walls to sterilize these lesions. The other tendency of tuberculosis to obstruct the bronchi with tracheobronchitis prevents the debris containing tubercle bacilli from being evacuated; this is also a big factor in reactivation. The extent of disease is a factor because the more extensive the disease, the greater the probability that these serious types of lesion are present. Since the type of disease present is the main factor in reactivation, our results are as expected. Minimal tuberculosis responds well to drugs only, with no reactivations. In moderately and far advanced disease those patients with resection of

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these serious types of lesion have fewer reactivations than those who received drugs only. With anteroposterior tomographs, bronchography and bronchoscopy, using right-angle and fore-oblique telescopes, most of these serious types of disease can be detected, and it is the physician's responsibility to rule out or remove such lesions before the patient is discharged. Patients have positive gastric cultures for a year or more before they admit having sputum or have x-ray film evidence of new disease, and gastric cultures are necessary to detect early reactivation. The old ideas that physical exertion, pregnancy, etc., are causes of reactivation are untenable.—A. R. Allen: *Dis. Chest*, 33: 275, 1958.

SURGICAL TREATMENT OF PULMONARY HÆMORRHAGE IN TUBERCULOSIS

In most instances, pulmonary hæmorrhage due to tuberculosis ceases with proper medical therapy; the setting for recurrent and uncontrollable hæmorrhage is to be found in the patient who has a thick-walled cavity. A report of one lobectomy and two pneumonectomies for the control of pulmonary hæmorrhage, in the presence of thick-walled cavities, is presented by Ford *et al.* (*J. Thoracic Surg.*, 35: 341, 1958). Twenty-one instances of fatal pulmonary hæmorrhage were reviewed. It was felt that seven patients might have been saved by pulmonary resection on the basis of current surgical considerations. Medical, surgical, and anæsthetic considerations in the patients with pulmonary tuberculosis and hæmorrhage are discussed.

BILATERAL MIDDLE LOBE SYNDROME

Obstructive pneumonitis of a lobe or segment may be caused by an intrinsic lesion such as mucosal œdema, fibrosis or plugging, or by extrinsic compression from lymph nodes or tumour. The right middle lobe is the most susceptible, the lingula being the next most frequently involved.

The term "bilateral middle lobe syndrome" is used by Webb (*Dis. Chest*, 33: 268, 1958) to describe concomitant chronic obstructive pneumonitis of the right middle lobe and its homologue, the lingula, and two cases are presented, which are the first reported to have undergone bilateral resection for this condition.

The etiology of nontuberculous bronchiectasis and the middle lobe syndrome is probably similar in that some degree of bronchial obstruction plays a prominent role in each. However, the middle lobe syndrome usually develops in older people and is associated with chronic lobar pneumonitis—infrequent in the case of bronchiectasis. The middle lobe syndrome apparently persists as chronic pneumonitis because bronchial obstruction is more prolonged or permanent, while in bronchiectasis obstruction is transient or partial.

Present evidence suggests a tuberculous origin of the compression collar of enlarged nodes around the middle lobe bronchus in many cases. Right middle lobe atelectasis is common in elderly

patients, secondary to reactivation of quiescent tuberculous adenitis which produces gradual compression and frequently perforation of the bronchi. However, many other cases have been found in which tuberculosis was excluded and the nodes were hypertrophied from non-specific inflammation.

Symptomatology is related to bronchial narrowing, leading to recurrent attacks of pneumonia and frequently symptomatic bronchiectasis. There is usually a chronic cough, often spasmodic, occasionally severe, and intermittently productive. Blood streaking or frank hæmorrhage is common, due either to the bronchiectasis or to bronchial ulceration by calcified lymph nodes. Persistent wheeze over the affected lobe is suggestive of this diagnosis. Bronchoscopy may show bronchial narrowing, though often the stenosis is located distally and is demonstrable only by bronchograms or laminograms. Treatment depends on many factors, such as chronicity of the process, symptomatology, and age and general condition of the patient. Early cases, especially with modern antibiotic therapy, may be completely reversible. In any chronic case, only resection is curative. However, as many chronic cases are completely asymptomatic and have remained so under observation for many years, the desire for radiologic improvement must be tempered by full evaluation of the patient.

MYOCARDIAL ATROPHY IN CONSTRICTIVE PERICARDITIS

Whether myocardial atrophy actually is present in constrictive pericarditis is controversial. Because of this disagreement, Dines and his colleagues felt that a pathologic investigation was warranted. Their basic plan was to study the myocardial fibres in constrictive pericarditis with particular regard to thickness, and to compare the thickness of the muscle fibres in constrictive pericarditis with the thickness of those from normal hearts and those from hearts affected with other forms of chronic pericardial compression, namely chronic exudative pericarditis and chronic pericardial effusion.

Eleven cases of constrictive pericarditis, one case of chronic exudative pericarditis, and two cases of chronic pericardial effusion were studied at necropsy. By micrometer measurements of the diameter of the myocardial fibres, definite muscle atrophy was found in the 11 cases of constrictive pericarditis and in two cases of chronic pericardial effusion when compared with specimens from normal controls in which the age and sex were the same as in the cases of pericarditis. The myocardial atrophy appeared uniformly throughout the myocardium, presumably because of the prolonged pericardial compression. In exudative pericarditis of several weeks' duration, the atrophy was limited to the edge of the myocardium near the epicardium; the remainder of the myocardium was normal. These findings constitute an adequate explanation for the continuing improvement in myocardial function months and even years after pericardiectomy.—*Proc. Staff Meet. Mayo Clin.*, 33: 93, 1958.

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MEDICAL NEWS *in brief*

RESPIRATORY VIRUSES AND HEART DISEASE

On the basis of the study of 21 cases of myocarditis and two cases of pericarditis, Silber (*Ann. Int. Med.*, 48: 228, 1958) presents data in support of the thesis that a virus, and especially the virus of influenza, is a cause of acute and even of chronic heart disease. The causative agent was identified by the demonstration of specific antibodies for the virus of influenza or of psittacosis, or the presence of cold hæmagglutinins. The relation between an antecedent upper respiratory infection and the subsequent myocarditis is commonly ignored because of the prolonged time interval separating the two. Other important clinical aspects noted included the following: diastolic as well as systolic murmurs could be heard over the precordium during the course of the myocarditis. Sensitivity to digitalis provided an important index of the presence of myocarditis. No specific ECG configuration could be found to indicate a viral myocarditis. Chronic left heart strain is possibly an ECG residual of preexisting myocarditis.

It is concluded that cases presenting clinical characteristics compatible with the diagnosis of "postpartum cardiac disease", Fiedler's myocarditis, benign idiopathic pericarditis, endocardial fibroelastosis, or idiopathic ventricular hypertrophy may occasionally be the result of a viral infection of the myocardium.

PAINFUL NONSUPPURATIVE SWELLING OF COSTOCHONDRAL CARTILAGES (TIETZE'S SYNDROME)

Karon *et al.* (*Proc. Staff Meet. Mayo Clin.*, 33: 45, 1958) report 13 cases of Tietze's syndrome (benign, painful, nonsuppurative swelling of one or more of the costochondral cartilages) encountered during 1955 and 1956; the clinical features, etiologic possibilities, and differential diagnosis of this syndrome are reviewed. Treatment is nonspecific, but it is suggested that infiltration of hydrocortisone or related steroids into the involved site may afford prompt relief for patients with persistent discomfort. This syndrome is perhaps more common than reports in the literature would indicate, and should be considered in the differential diagnosis of chest pain, especially when heart disease is suspected.

ATRIAL SEPTAL DEFECT IN THE AGED

Atrial septal defect is the form of congenital heart disease most commonly encountered in elderly subjects. Kelly (*Ann. Int. Med.*, 2: 267, 1958) describes a series of 19 patients over the age of 47 with this disorder. Only three instances of other congenital malformations of the heart were recognized in subjects of the same age range during the period of observation. A long, active life is possible with this disorder. The diagnosis can usually be suspected without difficulty on clinical ex-

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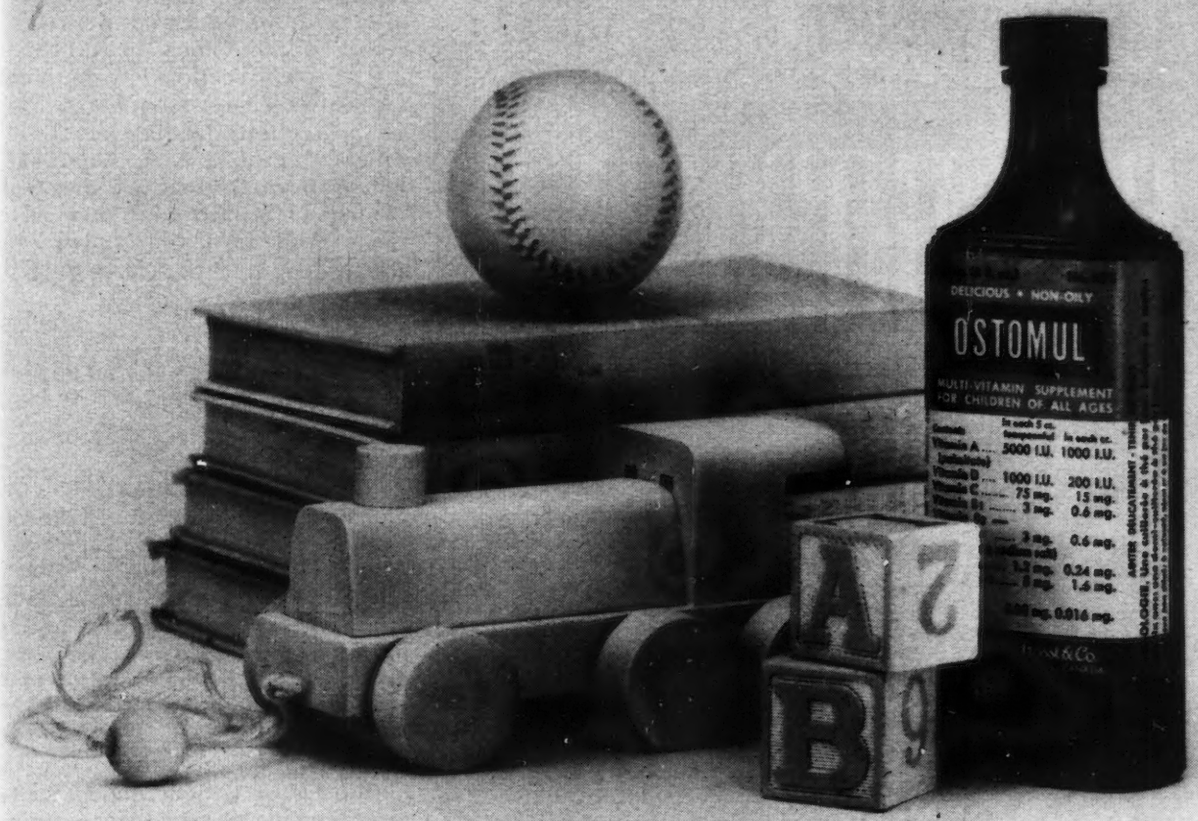
SOUGHT FOR IN...THE GROWING INFANT AND CHILD..."

Spies, T.D.: J.M.A. Alabama 26:193, Feb., 1957.



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Vitamin A	5000 Int. Units
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Vitamin B_1	3 mg.
Riboflavin	3 mg.
Niacinamide	8 mg.
Pyridoxine HCl.	1.2 mg.
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Bottles of 4, 8 and 16 fluid ounces.

DOSAGE: One teaspoonful (5 cc.) daily. Children under six years of age, one-half teaspoonful daily.

ALSO AVAILABLE . . . when vitamins A, D and C alone are required . . . or for added economy.

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Each (5 cc.) teaspoonful provides:

Vitamin A	5000 Int. Units
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Vitamin C	75 mg.

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SYNONYM FOR SERVICE TO CANADIAN PHYSICIANS SINCE 1899

MEDICAL NEWS *in brief*

(Continued from page 44)

amination. Hæmodynamic data are presented which suggest that high pulmonary blood flow over a long lifetime does not necessarily result in pulmonary hypertension.

The complications of an atrial septal defect are frequent respiratory infections leading to chronic lung disease, and pulmonary hypertension leading to right ventricular failure and reversal of the shunt. An infrequent but serious complication is pulmonary artery thrombosis.

OKLAHOMA COLLOQUY ON ADVANCES IN MEDICINE

The Second Oklahoma Colloquy on Advances in Medicine will be held on November 12, 13, 14 and 15. It will be devoted to Arthritis and Related Disorders and is under the joint sponsorship of the Department of Medicine, University of Oklahoma, the Division of Postgraduate Education, Geigy Pharmaceuticals, Wyeth Laboratories, The Upjohn Company, Pfizer Laboratories, and Schering Corporation. Twelve nationally prominent investigators in their field will participate and present the results of original work from their laboratories.

Registration will be open to all physicians. Further information may be obtained by writing to the Division of Postgraduate Education, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma.

OTOLARYNGOLOGIC ASSEMBLY

The University of Illinois College of Medicine Department of Otolaryngology announces its Annual Otolaryngologic Assembly from September 29 to October 5, 1958. The Assembly will consist of an intensive series of lectures and panels concerning advancements in otolaryngology, and evening sessions devoted to surgical anatomy of the head and neck and histopathology of the ear, nose and throat.

Interested physicians should write to the Department of Otolaryngology, 1853 West Polk Street, Chicago 12, Illinois.

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"...NUTRITIVE FAILURE SHOULD BE VIGOROUSLY SOUGHT FOR IN...THE AGING AND THOSE WITH ANY TYPE OF UNDERLYING CHEMICAL IMBALANCE..."

Spies, T.D.: J.M.A. Alabama 26:193, Feb., 195

— to prevent or correct vitamin deficiency in the adult or aging patient —

when diet is restricted — as in peptic ulcer, colitis, diabetes mellitus, chronic alcoholism, nephritis and heart disease, food faddism, anorexia nervosa.

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when requirements increase — as in acute infections, after surgery, in hyperthyroidism, in debilitating diseases such as tuberculosis, arthritis, and chronic asthma.

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Vitamin B_1	5 mg.
Riboflavin	3 mg.
Niacinamide	12.5 mg.
Pyridoxine hydrochloride	1 mg.
Vitamin B_{12}	1.5 mcgm.
Vitamin C	35 mg.
Vitamin D	500 Int. Units

DOSAGE: For prophylaxis: one or two tablets daily. For therapeutic use: one or two tablets two or three times daily.

Bottles of 30 and 100 tablets.

Charles E. Frosst & Co. MONTREAL, CANADA

SYNONYM FOR SERVICE TO CANADIAN PHYSICIANS SINCE 1899

MEDICAL NEWS *in brief*

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CARD FOR PATIENTS ON ANTICOAGULANT THERAPY

An "emergency" identification card for the protection of patients on long-term anticoagulant therapy is now available to physicians from the American Heart Association and its affiliates.

The card, designed as a wallet insert, was developed as a result of requests from physicians seeking to protect their patients on anticoagulants in case of accident, dental surgery or other treatment that may induce bleeding. It points out that the bearer "is being treated with anticoagulants which slow down clotting of the blood." In case of emergency—bleeding, injury or illness—the card advises that a doctor be called, since the patient may require an antidote.

The card contains space for the name, address and phone number of the individual's physician. There is also space to indicate the kind of anticoagulant prescribed and the patient's blood type. The card was designed with the approval of the Committee on Prothrombin Determinations of the American Heart Association.

In addition to making the anticoagulant identification card available to physicians, the Heart Association also is calling it to the attention of dentists, hospital emergency room personnel, nurses, police and others who most commonly handle emergencies.

Physicians may obtain samples of the identification card from their local Heart Association or from the American Heart Association at 44 East 23rd Street, New York City.

NEW DRUG FOR LEPROSY

A British journal, *Leprosy Review*, describes in its January 1958 number the results of clinical trials conducted by Dr. T. F. Davey, head of a research unit in Eastern Nigeria, with a diphenyl thiourea compound known as CIBA 1906, which has given very good results in treatment of leprosy. Experience has shown that the new drug has various advantages over former methods of treatment; it prevents scarring and disfigurement of the patient's skin and is also particularly valuable for treating children.

The report notes the excellent results obtained in Nigeria through close co-operation in leprosy control between government officials, WHO and UNICEF as well as missionaries.

MANAGEMENT OF THE COMPLICATIONS OF ACUTE NEPHRITIS IN CHILDHOOD

The complications of acute nephritis in childhood are uncommon but serious, and are outlined and discussed by Burke (*Proc. Staff Meet. Mayo Clin.*, 33: 23, 1958). These complications consist of electrolyte disturbances during the oliguric or anuric phase and the occurrence of hypertension and hypertensive encephalopathy. Fluid should be allowed orally or intravenously in calculated amounts for adequate replacement of insensible losses and losses from vomiting plus urinary losses. Fluids for intravenous administration, when necessary,

(Continued on page 54)

...VITAMIN INADEQUACIES ARE ROUTINE IN A SURPRISINGLY LARGE PERCENTAGE OF FAMILIES...

Dietary Levels of Households in the Northeast.
U.S. Department of Agriculture May, 1957.
U.S. Government Printing Office.

— to provide vitamin-mineral supplements for general family use

convenient . . . economical . . . provides essential vitamins and minerals to support general health and resistance.

"NEO-CHEMICAL FOOD"
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Each daily dose of 2 tabsules contains:

Ferrous sulphate BP	150 mg. (2½ gr.)
Copper sulphate	5 mg.
Magnesium stearate	12 mg.
Manganese carbonate	0.6 mg.
Vitamin A	2000 Int. Units
Vitamin D	2000 Int. Units
Bone flour	260 mg. (4gr.)
Vitamin B_1	2 mg.
Vitamin B_2—Riboflavin	2 mg.
Brewer's yeast concentrate	100 mg.
Niacinamide	10 mg.
Vitamin C (Ascorbic acid)	50 mg.
Potassium iodide	0.4 mg.

At daily cost of about 3½ to 7 cents.

DOSAGE: One or two tabsules daily.

Bottles of 50, 100 and 250.

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MEDICAL NEWS *in brief*

(Continued from page 52)

should consist of 10% solution of dextrose in water given in amounts ranging from 400 ml. per square metre per day in older children and infants. At times the fluids may contain 0.2% sodium chloride in an effort to lower the concentration of serum potassium. Serum potassium levels may rise to dangerous concentrations and predispose to cardiac arrest and death; hence, serial determinations of this substance and serial electrocardiograms are of clinical importance. Ion exchange enemas consisting of a solution of carboxylic acid resin are recommended as an aid in lowering the levels of serum potassium. Hypertension can be controlled by a daily intramuscular injection of a combination of reserpine and hydralazine in a dose of 0.15 mg. of each per kg. of body weight when blood pressure increases to more than 140 mm. Hg systolic and 100 diastolic.

ESSENTIALS OF PHYSIOLOGY*

When Bainbridge and Menzies' *Essentials of Physiology* first appeared it was intended for the simpler-minded medical student who found large texts overpowering. Strange to relate, many British medical students between the two wars contrived to pass their examinations using this book together with lecture notes, though this must have been far from the authors' intention. After a lapse of 17 years, "Bainbridge and Menzies" has been drastically revised and brought up to date. It would serve either as a text for pharmacy, physiotherapy or nursing students, or as a general introduction to the subject before use of a larger textbook.

*Bainbridge and Menzies: Essentials of Physiology. 10th edition revised by H. Hartridge and J. L. D'Silva. Longmans, Green & Co., Toronto, 1957. Price $6.50.

McEACHERN POSTDOCTORAL FELLOWSHIP

The first McEachern Postdoctoral Fellowship for advanced training and research in muscle disease has been awarded by the Muscular Dystrophy Associations of America to Dr. J. L. Connelly, a 30-year-old biochemist, currently a graduate fellow in the Department of Biochemistry, University of Rochester School of Medicine and Dentistry.

Dr. Connelly is planning to investigate the relationship of the thyroid hormone to respiration, and to the production of energy in mammalian tissues, at the Institute for Enzyme Research, University of Wisconsin, Madison.

The McEachern Fellowship is one of two established by M.D.A.A.; it is in honour of the late Dr. Donald McEachern, who was associate professor of neurology at McGill University, and a member of M.D.A.A.'s Medical Advisory Board. The other fellowship—named for the late Dr. Joseph L. Lilienthal—was awarded for the first time in November of last year.